FEB 4 1930

VOL. CLXXIX, No. 2 FEBRUARY, 1930 No. 695

Circulate only Overnight

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ESTABLISHED 1820

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1930

ORIGINAL ARTICLES.

SOME PRESENT-DAY CONCEPTS IN NEPHRITIS.*

By Herman Elwyn, M.D.,

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Introduction. Our understanding of Bright's disease has undergone considerable change in recent years. Many things have helped to produce this change. Not the least amongst these is a better knowledge of the normal functions of the kidneys, to the development of which so much has been added by the methods devised by Prof. A. N. Richards of this University. Chemical studies of the blood and the body fluids, detailed histologic studies of diseased kidneys, the routine use of the blood-pressure machine and the ophthalmoscope, have added to our understanding of the kidneys, and master clinicians have taught us how to correlate histologic changes in the kidneys with symptoms which are the expression of abnormal function. As a result, we have got away from old concepts current among clinicians of the older generation. We do not speak now of chronic parenchymatous nephritis and of chronic interstitial nephritis, the latter of which, as some one has said, is neither interstitial nor nephritis. Especially, we have drawn away from the clinical use of purely gross anatomic descriptions. We do not care now whether a kidney is white or red, large or small. Instead we have developed new concepts, and it is the meaning of some of these newer concepts that I want to discuss: The concept of renal insufficiency, what we mean by uremia, by nephrosis, especially lipoid nephrosis, and the concept of malignant renal sclerosis.

* Read before the Piersol Anatomical Society of the University of Pennsylvania, December 7, 1928.

I. **Renal Insufficiency.** *Insufficiency of an Organ.* We say an organ is insufficient when it is unable to perform the function for which it exists, in a complete manner. We speak of myocardial insufficiency, of liver insufficiency, as we speak of renal insufficiency. An organ performs its functions under a variety of conditions. The normal heart supplies the necessary amount of blood to maintain an adequate flow through the capillaries when the individual is at rest and when he is performing heavy work. If the heart is unable to supply a sufficient amount of blood when the individual is resting, we say that the heart is totally or markedly insufficient. If the heart supplies the necessary amount of blood when the person is resting but is unable to supply it when he is doing work, we say that the heart is relatively insufficient, or insufficient to a certain degree. We measure in a rough manner the degree of insufficiency by the difference between that which we know a normal heart can do and that which the particular heart under observation is actually accomplishing. To be able to measure this difference we must know the limitations of the normal heart and the maximum capacities which it possesses.

Similarly with the kidneys. If we are to estimate the degree of inability on the part of the kidneys to function properly, we must know what the normal kidneys can do. Frerichs, who was the greatest clinical teacher of his time, prefaced his book on Bright's disease with the motto taken from Marshall Hall: "To become good and enlightened practitioners, we must become able physiologists."

The Function of the Kidneys. The kidneys are the chief excretory organs of the body. As such it is their chief function to excrete the waste substances of metabolism, which cannot, like carbon dioxid, be excreted through the lungs, and which are not excreted through the intestinal tract. These are the waste substances of protein metabolism, namely, urea, uric acid and creatinin. The excretion of these substances is one of the functions of the kidneys. Another function is to play a part in certain of the regulatory mechanisms in the economy of the organism. The organism attempts to maintain constant values for those substances which it needs in its economy, and for those processes to which it has become adapted in phylogenetic development. In the words of Claude Bernard, it attempts to maintain a constant internal milieu in contrast to the ever-changing external milieu. A part of this internal milieu is a constant water content of the organism, especially of the blood, which the organism attempts to maintain by means of a regulatory mechanism. This mechanism has for its effector organs the water depots of the body, chief of which are the skin and the muscles, and the kidneys which excrete the water. A large amount of water when taken into the alimentary tract is soon absorbed from there into the blood stream. The blood is diluted temporarily and the water soon passes into the water depots, from where it is gradually

returned to the blood stream. Within one-half to three-quarters of an hour after the intake of the water, the kidneys begin to eliminate the excess of the ingested water. This whole mechanism is presided over by a regulatory center, and sufficient evidence is accumulating for the definite localization of this center in the hypothalamic region of the brain. The studies of Marx and of Siebeck have shown that the curve representing the dilution of the blood following the intake of water is the same whether 1000 cc. or only 50 cc. have been taken. Marx found that the curve of blood dilution can be obtained without the drinking of water when a susceptible person is in a hypnotic trance, simply by suggestion that the person is drinking water.[1]

The function of the kidneys as part of this mechanism for water regulation is to excrete the excess of water presented to it by the blood stream. But, when the water of the organism, especially of the blood, is in danger of being diminished below the normal limit, it is also the function of the kidneys to reduce its excretion to the very minimum necessary to keep the waste substances in solution.

A third function which the kidneys exercise is in helping to maintain the normal acid-base balance in the internal milieu. For the maintenance of this balance there are other mechanisms in the body, and the kidneys add their help. When an excess of acid is present in the body they retain base by the excretion of acid phosphate. It is possible that ammonium, which the organism makes use of to neutralize acid, is formed in the kidneys themselves.

The Maximal Capacity of the Kidneys. Of these three functions, namely, the removal of the waste substances of protein metabolism, the regulation of the water content of the blood and the regulation of the acid-base balance in the body, the second one mentioned, that of water regulation, is the most sensitive function. The kidneys react very quickly to any disturbance in water regulation. Whenever water is being lost from the blood stream by other channels the excretion of water through the kidneys is diminished to an extreme degree, although the waste substances accumulate in the blood. Thus, it is this function of water excretion which can most easily be made use of to estimate what the functional abilities of the kidneys are.

The largest amount of water which the kidneys can excrete continuously is probably very difficult to estimate. Cushny puts it at 1 liter an hour. Cases of diabetes insipidus, in which 20 liters of urine have been eliminated in one day, have been reported. Cases in which 12 liters a day are excreted are more frequent. We can, therefore, say that the elimination of 1 liter of water in two hours is within the functional capacity of the normal kidneys. Although this is probably not the maximal ability of the kidneys, we may make use of it as such, and we may rightfully assume that normal kidneys are able to eliminate this amount in the time mentioned. It is a

matter of frequent observation at the present time that in normal individuals the intake of 1 liter of water is followed within two and a half to three hours by its elimination, and diuresis begins one-half to three-quarters of an hour after the intake. The functional ability of the kidneys to excrete promptly an excess of water has been made use of in the so-called water test of Volhard: 1500 cc. or, better still, 1000 cc. are taken on an empty stomach and the time of its elimination observed. We expect it to be completely eliminated in two and a half to three and a half hours. This is what we assume, in a practical way, to be the maximal limit of what the normal kidneys can do in regard to their most sensitive function in one direction.

In another direction, in preventing the elimination of water when the water content in the blood threatens to be reduced, the kidneys are equally efficient. The non-elimination of water may go on to complete suppression of urine when there is extreme loss of water through other channels, such as occurs in cholera. When this occurs the waste substances are not eliminated from the blood. Ordinarily, however, starting with the normal water content of the organism, when water is withheld for twenty-four hours, the waste substances in the blood are excreted completely, but in as little water as is necessary to keep them in solution. This is familiar to us in the concentrated urine observed normally when we sweat a good deal and do not drink sufficient water to make up for the loss, and in the concentrated urine in fever. The degree of concentration has its limits, and as we measure the concentration by the specific gravity of the urine this limit is easily ascertainable. In fact, we know that in the protein and sugar-free urine the specific gravity rarely reaches above 1030 to 1036. In practice, we take these figures on the expression of the maximal ability of the kidneys to conserve water for the organism and still excrete completely the waste substances of protein metabolism.

We have then, as the expression of the maximal capacities of the normal kidneys, the ability to excrete a given amount of water in a certain limited period; their ability to conserve water for the organism by excreting the waste substances in a definitely concentrated form.

The manner in which the kidneys perform this function is familiar to us. In the arterial system of the kidneys there is interpolated an enormous capillary surface in a very compact form—the glomeruli. As the blood passes over this capillary surface, a de-proteinized solution containing the other constituents of the blood plasma passes through these capillaries and their covering membrane of Bowman's capsule. In addition to the blood pressure, which helps to separate this solution from the proteins of the blood plasma, its passage through the glomerular membrane follows, in all probability, those laws which govern the passage of solutions through

any living membrane of many layers, laws which have recently been studied by Wertheimer in Abderhalden's laboratory, and by others. The passage of such solutions through living membranes is evidently different from filtration and diffusion through a dead membrane.

This enormous capillary surface is obviously not always open in its entirety for the passage of blood over it. For, if we assume that all the capillaries of the glomeruli are open when the kidneys are excreting ½ liter per hour, it is evident that they cannot also all be open when the kidneys are excreting only ½ liter in twelve hours. The fact that only a limited number of capillaries are open at one time, and that the number of open capillaries is dependent upon the amount of water which the kidneys have to excrete, has been demonstrated by Professor Richards. The ability of the kidneys to vary the number of active glomeruli, and of active capillaries in a single glomerulus, explains their ability to adapt themselves to all the changes which threaten the water content of the organism and especially of the blood.

When the protein-free solution has passed out of the arterial system, it again passes over an enormous surface—the lumen of the convoluted tubules, the cells of which abstract and absorb those substances which the organism needs in its economy, namely, water, sugar, salt and base. The longer the solution remains in contact with the cells of the tubules, the more water will be absorbed and the more concentrated is the final product. The loop of Henle acts as a pressure reservoir which serves to keep the solution in contact with the cells for a longer period. The greater the amount of the protein-free solution passing through the glomerular capillaries, the greater will be the flood coming down the tubules, the smaller will be the amount absorbed by the cells of these tubules. With a smaller amount coming down, the fluid moves with less speed, more water is abstracted and the final product is more concentrated. The ability of the kidneys to concentrate the urine to a maximum degree is, therefore, dependent (1) on the glomeruli which limit the amount of fluid passing through their capillaries, and (2) upon the maximal absorption by the cells of the convoluted tubules.

So far we have spoken of the maximal ability of the kidneys as expressed in its most sensitive function, that of helping to maintain the volume and water content of the blood within normal limits. What is the minimum which is required of the kidneys?

The Minimum Required of the Kidneys. In their function to help maintain the blood volume, the kidneys constitute one of many organs. In the excretion of the waste substances of protein metabolism the kidneys alone are concerned, for the excretion of urea through the skin is minimal and of no practical importance. We must, therefore, demand of the kidneys that they excrete under all possible conditions these waste substances, urea, uric acid, creatinin

and perhaps some undetermined substances which make up the rest of the undetermined portion of the total nonprotein nitrogen of the blood. This is the minimum which the kidneys must do. The normal kidneys have no difficulty in excreting these substances even with a maximal protein intake, and even the ingestion of large amounts of urea is quickly followed by their elimination.

When is the minimal limit reached? How much kidney substance can be lost or destroyed, and the rest of the kidneys still be able to excrete the waste substances of protein metabolism from the blood? The factor of safety varies with the individual organ, and it has been shown experimentally on animals that with the removal of almost two-thirds of kidney substance, the rest is still able to excrete all of the waste substances from the blood. When more kidney substance is destroyed the waste substances cannot be excreted and accumulate in the blood.

Renal Insufficiency. Our understanding, then, of normally and sufficiently functioning kidneys is, that the kidneys are able to excrete an excess of water in a certain minimum period of time; that they are able to concentrate the urine to a certain maximum degree; that they are able to eliminate the waste substances under all possible conditions of protein intake. The kidneys are insufficient when they are unable to do this, that is, when they are unable to concentrate the urine to a certain maximum degree; when they are unable to excrete the waste substances under all possible conditions.

The function of excreting the waste substances, being the minimal requirement for the normal functioning of the kidneys, is last to diminish. When this function is lost to a degree where, with the intake of a minimum amount of protein necessary to replace the wear and tear of the body, the waste substances are not eliminated, the kidneys are totally or completely or absolutely insufficient. The evidence and the measure of this absolute insufficiency is the amount of the waste substances, namely, the total nonprotein nitrogen, and the urea, uric acid and creatinin, in the blood.

Between the normally functioning kidneys and the absolutely insufficient kidneys indicating the destruction of at least two-thirds of functioning substance, there is a wide field. All grades of prolongation of water excretion above the minimum requirements and all grades of diminution in the ability of the kidneys to concentrate the urine occur with kidneys which are still able to excrete the waste substances of protein metabolism. We speak of such kidneys as being relatively insufficient or insufficient to a certain degree, and we use especially the maximum concentration of the urine to designate the degree of renal insufficiency. When the highest specific gravity of the urine cannot go above 1018 we know that the kidneys are insufficient to that degree, although the waste substances are completely eliminated.

Relative renal insufficiency is thus dependent upon the exclusion

of a certain number of glomeruli and of tubules from the functioning part of the kidneys. As this functioning part, the number of active glomeruli and tubules, becomes smaller and smaller, the elimination time of an excess of water becomes longer, and the ability to concentrate as measured by the specific gravity of the urine becomes less and less. When total insufficiency is reached the ability to concentrate has reached its lowest ebb. The specific gravity of the urine then remains fixed at about 1010 or 1012, and the molecular concentration of the urine is practically the same as that of the protein-free blood plasma.

Such is our present conception of renal insufficiency, relative and absolute. Aside from the chemical examination of the blood, the tests for determining renal insufficiency and its extent are very simple indeed, namely, the water and the concentration tests.

When do we find renal insufficiency? In its typical form we find it whenever there is a gradual destruction of glomeruli, and secondary to this the loss of the corresponding tubules. This is the case in chronic glomerulonephritis and in certain cases of diseases of the arteries and arterioles in the kidneys. We can follow here the gradual progress of relative insufficiency into absolute insufficiency of the kidneys. Renal insufficiency is, of course, also found in extensive destruction of the kidneys due to the so-called surgical diseases of the kidneys. We also find renal insufficiency whenever the blood plasma is prevented from reaching the filtering membrane in the glomeruli. This occurs: (1) In acute diffuse glomerulonephritis, where the glomeruli are filled with a cellular exudate which prevents the blood from passing through their capillaries in sufficient amount; (2) with a general contraction of the small arteries and arterioles in the kidneys, such as occurs in reflex anuria from a stone in the ureter, and in some cases of lead poisoning; (3) whenever water is diverted from the blood stream into other channels in large amounts, and the organism attempts to conserve its water by shutting the glomerular capillaries. This occurs in cholera, when water is lost from the body through the alimentary tract. It also occurs in high intestinal obstruction, where through the loss of water by vomiting and because of the paralysis of the splanchnic circulation, the water content of the blood threatens to become diminished. In such cases there is an increase in the waste substances in the blood, although the glomeruli are not diseased, but because the blood plasma is prevented from reaching the glomerular membrane through which the water must pass. In bichlorid of mercury poisoning there is often anuria, and with it there is, of course, renal insufficiency and the accumulation of waste substances in the blood. Here the glomeruli are not inflamed but are markedly congested, and it may be assumed that the mercury which like all heavy metals is a capillary poison has injured the glomerular capillaries to such a degree that they have lost their contractile

power. The blood passing through these capillaries passively dilates them, ruptures some of their walls, chokes most of them, so that blood circulation in the glomeruli soon ceases and glomerular filtration becomes impossible.

So much for the concept of renal insufficiency.

II. **Uremia.** Another concept in connection with diseases of the kidneys in uremia. Our conception of uremia has undergone considerable change in recent years, mainly as a result of the application of chemical studies of the blood and of routine blood-pressure examinations to clinical medicine. The term uremia literally means an increase of urea in the blood, and the earliest observers after Bright who found an increase of urea in the blood assumed that the clinical symptoms of uremia were due to this increase. It was found, however, that symptoms, especially of the central nervous system, occurred in Bright's disease whether urea was increased in the blood or not, and so the hunt began for some substance, the presence of which would explain the occurrence of all the various symptoms usually connected with the term uremia. Nearly all the various constituents of the blood plasma and of the urine were successively held responsible—urea, ammonium carbonate, uric acid, potassium salts, other salts, creatinin, various hypothetical organic substances, acid substances and many others. Even recently, a toxic base, which causes convulsions in guinea pigs, was held to be the causative agent of uremia.

It probably would have been better for the concept of uremia if the original assumption that the symptoms are caused by the retention of urea in the blood would have been adhered to. One of the reasons for rejection had been that many investigators had injected urea into the blood stream of animals and had found that it was quickly excreted without producing any symptoms. It seems laughable to us when we read that conclusions were drawn from the injection of 3 or 4 gm., even when injected after the extirpation of one kidney. At the present time 30 to 50 gm. of urea and even more are given by some clinicians in the treatment of edema without producing any symptoms and with the prompt elimination of the injected urea. Hence it is even now generally assumed that urea cannot be the substance causing uremic poisoning, since the ingestion even of large quantities does not cause any harm. This is true in persons with normal kidneys, but is it also true of the concentrations of urea found in the blood in the terminal stage of nephritis?

The Occurrence of Convulsions in Nephritis. The question, therefore, which arises in the observation of cases of Bright's disease is: Why do certain symptoms, coma and convulsions, occur in some cases of Bright's disease, whether the waste substances in the blood are increased or not, and why do they not occur in others in which the waste substances are also increased? In cases of anuria from obstruction of both ureters, in which all the urinary substances are

retained in the body, convulsions are uncommon and are not part of the clinical picture, and for many days the patient may not show any symptoms of poisoning.

Here the chemical studies of the blood, blood-pressure determinations and the observation of the retinal arteries in cases of nephritis have come to our help. We have definitely learned that convulsions do not belong to the clinical picture of poisoning by the waste substances, as in complete anuria. We have also learned that convulsions in nephritis are always preceded by a sudden rise in blood pressure; that accompanying the increase in blood pressure there is an arterial contraction which may be general, but which certainly occurs in the brain; that, as evidence for the occurrence of the arterial contraction in the brain we have the narrowed arteries in the retina which we can observe directly. We have learned that such a sudden increase in blood pressure, which is followed by tonic and clonic convulsions, or equivalent phenomena, such as sudden blindness and various forms of temporary paralysis or paresis, occur especially in the course of acute diffuse glomerulonephritis, or in the course of chronic hypertension, whether there is an increase in the waste substances of the blood or not. Ascoli, Strauss, and especially Volhard, have taught us to separate these convulsive seizures from true uremia. Even the name convulsive uremia should be abandoned and it is much better to speak simply of convulsions occurring in the course of acute or chronic nephritis.

True Uremia. With the separation of the convulsive phenomena from the clinical concept of uremia, there remain the symptoms which we connect with the retention of the waste substances in the blood, true uremia. We best gain an understanding of uremia when we follow the progress of absolute renal insufficiency in the course of chronic nephritis.

What strikes our notice at first in following a case of slowly progressive renal insufficiency is the pallor of the patient, as the basis for which there is a real moderately severe anemia. There is nothing specific in this anemia, but it commonly precedes the other symptoms and is of diagnostic value in calling attention to the possible presence of renal insufficiency. The anemia probably expresses a diminution in the regenerative powers of the hemopoietic apparatus.

As the waste substances in the blood increase in amount, the urea nitrogen which ordinarily forms about half of the total nonprotein nitrogen, now constitutes about 70 per cent. When the total nonprotein nitrogen in the blood reaches to about 100 mg. per 100 cc., all the tissues of the body contain a large amount of urea. The other waste substances in the blood, namely, uric acid and creatinin, are present in comparatively small amounts as compared to urea, and we can, therefore, neglect them as factors in the causation of uremic symptoms. The urea which diffuses easily

everywhere is present in every organ in excessive amounts. We now begin to notice symptoms due to the excretion of urea into the gastrointestinal tract. The presence of urea in the salivary glands leads to its excretion into the mouth, to its decomposition with the formation there of ammonium and to the odor of urine from the mouth. This leads to the presence of a disagreeable taste in the mouth, a coated tongue and anorexia. The presence of urea in the glands of the stomach leads to its excretion there, to the irritation of the mucous membrane of the stomach and to nausea and vomiting. The presence of urea in the glands of the intestinal tract leads to its excretion there, to the irritation of the intestinal mucous membrane, to diarrhea and to the formation of ulcers in the intestinal tract.

Increased excretion of urea through the skin also occurs, and itching is a frequent symptom, as is also an occasional dermatitis.

The gastrointestinal symptoms are frequently the only ones for a long period. As the urea nitrogen in the blood increases still more, all the organs in the body are practically saturated with urea. We now begin to notice the essential phenomena of true uremia, the symptoms due to retention of the waste substances in the tissues and organs, namely: (1) A gradually increasing narcosis, fatigue, drowsiness, stupor and eventually coma; (2) an increased irritability of the muscles, characterized by twitching of the muscles, tendon jumping and choreiform movements; (3) the gradual development of slow and deep breathing. Convulsions are not part of this picture, although convulsions do occasionally occur before death.

The slow and deep breathing is a phenomenon familiar to us. We recognize it as the breathing which we find in diabetic acidosis, and it is known by the name of its discoverer, Kussmaul. When we now examine the blood for its carbon dioxid content we find this to be reduced. There is a loss of alkali reserve. We know then that the third function of the kidneys, that of helping to maintain the acid-base balance in the body, has been lost. The kidneys are unable to excrete the fixed acids, and the retained acid phosphate deprives the bicarbonate of its base.

For the other two sets of symptoms, the mixture of narcosis and of muscular irritability, there is no definite and accepted explanation. Investigators are still looking for some mysterious poison. It seems to me that both of these sets of symptoms can be explained by the presence in the tissues of the enormous amount of urea. We must remember that, although urea is a harmless substance when it can be excreted within a short time, its continued presence in the tissues in such concentration as found in chronic uremia is an entirely different thing, and probably not at all harmless. Urea is known to have a narcotic effect on the central nervous system and derivatives of urea are made use of to produce narcosis in animals. In an experiment with some other object in mind, Gabbe found that

the presence of an increased amount of urea in a muscle caused an increased irritability of the muscle.

Experimentally, the problem has been attacked by the injection of urea into the blood stream of animals. Large quantities are necessary if the concentration in the blood is to remain high, and with normal kidneys it can only remain so for a short period. Among others, Leiter found that symptoms similar to uremia, although more violent, were produced by the injection of large amounts of urea in the blood. These experiments are, of course, not sufficient to settle this question. I think the point of attack must be a little different. In the experiment the kidney tissue should be removed to the extent where retention of the waste substances in the blood is just avoided. This should then be followed by the injection of urea into the blood stream and its concentration there should be maintained for a long time at a level corresponding to the figures found in uremia in man. Such experiments may eventually solve this problem.

In our present understanding of uremia there are thus involved two distinct concepts: One, which explains the appearance of convulsions and equivalent phenomena as the result of sudden arterial contraction in the brain, and occurring as an incident in the course of nephritis; the other, which explains the phenomena of true uremia as a result of the retention of the waste substances, chief of which is urea, in the blood. It is my own firm conviction that the phenomena of brain narcosis and increased muscular irritability are the result of poisoning by the large amounts of urea remaining for long periods of time in the respective organs.

III. **Nephrosis and Lipoid Nephrosis.** Another concept current at the present time is that of nephrosis, especially lipoid nephrosis. The term nephrosis is an unfortunate one, because it stands for two concepts, a pathological and a clinical. The term was first introduced by Müller, in 1905, to designate tubular degeneration in contradistinction to nephritis or glomerular inflammation. At that time it was not possible to separate clinically these two classes of kidney diseases. The term nephrosis does not appear again in the literature until Volhard and Fahr made use of it in their monograph in 1914. From then on it is current both clinically and pathologically

Volhard, who is a master mind in this field, clearly recognized the connection between glomerular inflammation and the accompanying clinical phenomena of hematuria, increase in blood pressure and renal insufficiency. It was, therefore, necessary for him to separate those cases in which inflammation of the glomeruli is not found, but which present clinical evidence of renal disease, such as albuminuria and edema. Volhard used the term nephrosis for this group of cases. It was a very mixed group, and the pathologic changes found in the kidneys included all the forms of tubular degeneration, albuminoid, hyalin, fatty, lipoid and amyloid degen-

eration and necrosis of the tubules such as is found in bichlorid of mercury poisoning, all without any histologic evidence of inflammation in the glomeruli. Fahr, the pathologist, used the term nephrosis to include all these forms of degeneration and also necrosis.

It is obvious that as a pathologic concept the term nephrosis is not as good as the term tubular degeneration. Also, necrosis is really not degeneration, so that both Fahr and Volhard spoke of specially characterized nephrosis, necrotizing nephrosis. The term nephrosis, however, has come to stay and when used in the pathologic sense as including various forms of degeneration or necrosis which are found histologically, we have no fault to find with it. It is quite another thing when we attempt to correlate all these forms of degeneration with clinical pictures. In febrile diseases we often find clinically a mild albuminuria and cloudy swelling of the cells of the tubules histologically. To speak, therefore, of the nephrosis of typhoid fever or of pneumonia, is to raise an unimportant clinical symptom to the dignity of a disease. In addition, we must not forget that albuminuria is a glomerular symptom. The proteins of the blood pass into the urine through the glomeruli and not through the tubules. In amyloid disease we have amyloid deposits in the glomeruli also. Fatty degeneration of the cells of the tubules in Graves' disease does not cause any renal symptoms; similarly glycogen deposits in the cells of the tubules do not cause any symptoms. In bichlorid of mercury poisoning there is necrosis of the cells of the tubules, and there is only congestion in the glomeruli. Here, however, hematuria occurs as well as anuria, both of which are glomerular symptoms, and sometimes with the anuria there is an increase in blood pressure.

We must, therefore, be very careful in attempting to correlate tubular degeneration with clinical phenomena. We may, however, use the term nephrosis in a clinical sense, and include under this term, not all possible forms of tubular degeneration in the manner of the pathologist, but a certain small well-defined group of kidney diseases. This group includes the bichlorid of mercury kidney, amyloid disease of the kidneys, possibly also the kidney of pregnancy, and the disease now called lipoid nephrosis. These four diseases of the kidneys have distinct clinical pictures, in the case of amyloid disease perhaps not so distinct, and they have this in common, that the glomeruli do not show any inflammatory changes. My own opinion is that it is much better to characterize each disease especially as I have done, and speak of the bichlorid kidney, the amyloid kidney and the kidney of pregnancy instead of speaking of them as nephrosis.

Lipoid Nephrosis. This brings us to lipoid nephrosis. It was particularly this disease which lead Volhard to revive the term nephrosis. Among his material there was a group of cases which presented a distinct and definite clinical picture—oliguria with

marked albuminuria; marked edema with hydrothorax and ascites; increase of lipoids in the blood; absence of hematuria, of hypertension and cardiac hypertrophy and of renal insufficiency. The cases began insidiously, ran a chronic course and most of them terminated fatally with pneumococcus peritonitis. On examination, the glomeruli were found to be normal and lipoid deposits were found in the cells of the tubules and in the interstitial tissue of the kidneys.

The necessity of separating these cases from similar ones with hematuria, hypertension and renal insufficiency, led Volhard to classify them as cases of nephrosis. Because of the absence of a definite etiology, and because of the distinctive clinical picture, he spoke of them as "genuine" nephrosis, also as chronic cases of nephrosis. Munk, who had seen similar cases, found lipoid granules in the urine, and lues as an etiologic factor. In this country Epstein, who had seen similar cases, found a reduction in the proteins of the blood. The reduction is in the albumin fraction of the proteins, the globulin remaining normal or becoming increased. He also found an increase in the cholesterol of the blood. These observations were corroborated by others. Because of the presence of lipoids in the urine and in the kidneys, and because of the increase amount of cholesterol in the blood, Munk used the term lipoid nephrosis to characterize this disease. Others, including Fahr, have accepted this term. This term simply denotes a certain symptom complex and has no connotation indicative of pathogenesis or etiology. The presence everywhere of lipoids is, in all probability, a secondary characteristic in the course of the development of the disease.

We have thus among our concepts of kidney diseases two which are designated by the term nephrosis: (1) A pathologic concept, which includes all forms of degeneration, but which adds nothing to our understanding of kidney pathology; (2) a clinical concept which includes certain definite clinical entities, which are characterized best, however, by other terms, with the exception of one form which we have called lipoid nephrosis, and which presents a definite symptom complex.

I say symptom complex advisedly. For it frequently happens that we have under observation a case of renal disease, presenting all the symptoms of lipoid nephrosis, namely, marked albuminuria, oliguria, marked edema, lipoids in the urine, increase of cholesterol in the blood, diminution of albumin in the blood and the absence of hypertension and renal insufficiency, only to find after one or two years or even sooner, that hypertension and renal insufficiency supervene. Here we have the symptom complex of lipoid nephrosis as a transitory phase in the course of chronic glomerulonephritis. In fact, this symptom complex is much more frequently found in the course of subchronic and chronic nephritis than as a disease by itself. Pure lipoid nephrosis is a rare disease. Fahr was only able

to examine the kidneys of 9 cases up to 1922. The disease does occur, however, and seems to be more common in children.

When we meet this symptom complex of lipoid nephrosis without evidence of chronic nephritis, we are, of course, unable to tell whether we are dealing with pure lipoid nephrosis or with this symptom complex occurring as a transitory phase in the course of chronic nephritis. Only the eventual course of the disease can determine definitely the diagnosis. For the last four years I have been having under observation a patient, presumably with lipoid nephrosis, who has at various periods taken as much as 3 to 4 gm. of thyroid extract for the treatment of his edema. I am still not sure whether I am dealing with a case of pure lipoid nephrosis or whether the symptoms of chronic nephritis will not eventually appear.

The Pathogenesis of Lipoid Nephrosis. I think that the pathogenesis of a symptom complex such as that of lipoid nephrosis, occurring sometimes in pure form, and at other times in combination with nephritis, is probably the same in each case. Occasionally one has the opportunity to observe a case of acute diffuse glomerulonephritis which subsides and is followed months later by the development of all the phenomena of lipoid nephrosis. This has been my experience as well as that of others. It seems to me that as a result of the acute diffuse nephritis, the glomerular membranes consisting of the capillary walls and the covering layer of Bowman's capsule have lost their function of holding back the proteins of the blood from passing through them, even though the exudate in the glomeruli has been absorbed, and the acute nephritis apparently healed. As a result of this loss of function, there remains a marked albuminuria in such cases, and the loss of albumin from the blood becomes so large that the reduction in the blood is noticeable. The organism attempts to replace the albumin lost from the blood plasma by the production of globulin which has a larger molecular aggregate and is more easily held back by the glomerular membranes. When the organism is able to do this the globulin in the blood plasma is increased, and, in fact, a slight increase in globulin is characteristic of this disease. Salvesen reported an interesting case, in which the loss of large amounts of albumin in the urine was accompanied by an increase in the proteins of the blood to as high as 10 per cent, of which the greater part was globulin.

When the organism is unable to compensate the loss of albumin by a corresponding increase in globulin the proteins of the blood remain at a low level. The inability on the part of the organism to regenerate the lost protein seems to be the result of a general depression of many vegetative functions, including the oxidative functions of the cells. This finds expression in the lowered basic metabolic rate and in the lowered resistance to infection. The increase of cholesterol in the blood is probably a secondary phenomenon due to a disturbance of nutrition in the cells, such as occurs also in diabetes.

When the organism is thus unable to replace the lost protein by the production of new, it attempts to limit the loss through the kidneys by limiting the amount of urine. A diminution in urine is characteristic of lipoid nephrosis. With a normal water intake and the diminution in the amount of urine, there is soon an increase in the water content of the body. With the water content of the blood remaining normal, the excess must accumulate in the tissues and hence the edema.

We can thus explain the various manifestations of the symptom complex of lipoid nephrosis, as the consequence of the continued loss of albumin, as the result of the inability on the part of the organism to replace the lost albumin, and as a result of the depression of certain vegetative functions. The loss of albumin must necessarily be due to some defect in the glomerular membrane through which the albumin passes. This defect can be ascribed to a previous acute nephritis which has healed but has left the glomerular membrane permanently defective, even when no such defect can be found histologically. The result is a case of pure lipoid nephrosis. The toxin of lues may possibly have a similar effect on the glomerular membrane.

An acute diffuse nephritis which does not heal completely, but passes gradually into the subchronic or chronic forms, may have the same effect in damaging the glomerular membrane. The consequence is a continuous marked albuminuria, and, secondarily, the development of the symptom complex of lipoid nephrosis. In this case, however, this symptom complex occurs in the course of subchronic or chronic glomerulonephritis.

IV. **Benign and Malignant Renal Sclerosis.** Another concept in modern use is that of renal arteriolosclerosis without renal insufficiency and with renal insufficiency, or benign and malignant renal sclerosis. This concept is also of recent development, and to understand it we must know how the groups of cases included under the term of arteriolosclerosis came to be separated from other groups of Bright's disease or nephritis. The pathologic anatomy of nephritis has its foundation in the work of Loehlein. In 1907 Loehlein published a study of 30 cases of nephritis in which the importance of the glomeruli in the pathology of nephritis was definitely established. Loehlein showed that all the forms of nephritis which we now call glomerulonephritis have their beginning in an acute diffuse inflammation of the glomeruli. He showed further that all cases of glomerulonephritis which are of longer duration than the acute form fall in three groups. The cases of the first group have a short and stormy course. These cases correspond to our conception of subacute diffuse glomerulonephritis, and end fatally within a few months. In the cases of the second group the character of the disease is milder and the duration is longer. These cases correspond to the subchronic form and last longer than a few

months, even as long as one or two years. The cases of the third group run a very chronic course from a few years to as much as twenty-five years.

These groups, the acute, the subacute, the subchronic and chronic forms of diffuse glomerulonephritis, together with the relatively benign focal glomerulonephritis, constitute by far the greatest number of cases included under the term nephritis. All these cases present inflammatory changes in the glomeruli, exudative and proliferative in the acute and subacute forms, with the addition of hyalinization and obliteration of the glomeruli in the chronic forms.

The recognition and separation of these groups of cases pathologically was accomplished by Loehlein and corroborated by others. Their clinical separation and their recognition as clinical entities was especially aided by Volhard.

Renal Arteriolosclerosis. With the separation of these groups of cases there remained one group, the cases of which also showed obliteration of the glomeruli. Some of the cases of this group were accompanied by total renal insufficiency, while others were not. In addition to the obliteration of the glomeruli there was also found marked arteriosclerosis of the small arteries and arterioles. The importance of the renal vessels in the pathology of Bright's disease had been recognized long ago by Gull and Sutton. They found a hyalin-fibroid substance in the muscularis of the small arteries and in the walls of the capillaries, and characterized the disease as a generalized arteriocapillary fibrosis. The arterial changes in the kidneys were further studied by Ziegler, who showed the importance of arteriosclerosis in kidney disease. But it was only with the recognition and separation of the diseases of the kidneys due to the inflammation of the glomeruli, that the importance of the arterial changes for the remaining group of cases was recognized. The pathology of arteriosclerosis of the kidneys was studied by a group of pathologists, among whom the names of Jores, Loehlein, Aschoff, Fahr and Herxheimer stand out preëminently.

It was established that in certain kidneys in which the glomeruli are not inflamed, there is found a hypertrophy and thickening of the walls of the small arteries and arterioles, hyalin and fatty degeneration of the thickened intima and narrowing of the lumen of these vessels. It was also found that as a result of extreme narrowing and complete occlusion of the small arteries, such as the interlobular arteries and the afferent arteries of the glomeruli, the corresponding glomeruli do not receive blood, become collapsed, then surrounded by connective tissue and finally completely obliterated. The cause of the obliteration of the glomeruli is evidently to be found in the occlusion of the small arteries and the arterioles. Individual investigators applied different names to these forms of kidney diseases, and we read of nephrosclerosis, nephrocirrhosis arteriolosclerotica, arteriosclerosis of the kidneys and renal arteriolo-

sclerosis. All these names meant to convey that there is a reduction of kidney volume as a result of arterial change. The important element, however, is the arterial change and not the reduction in kidney substance. The term renal arteriolosclerosis conveys this meaning and it has become one of our concepts in diseases of the kidney.

So far the concept of renal arteriolosclerosis had only a pathological meaning. It remained for a clinician—Volhard—working in conjunction with a pathologist—Fahr—to give the concept a clinical meaning. Volhard demonstrated that certain cases in which the kidneys show arteriolosclerosis with obliteration of some of the glomeruli, without any inflammatory changes in them, and with a greater number of glomeruli not at all affected, run a clinical course with the prominent symptom of chronic hypertension without the presence of renal insufficiency. These cases of chronic hypertension, of which we see so many and which are familiar to all of us, have been known to us under various names, such as benign hypertension, essential hypertension, the presclerosis of Huchard, the hyperpiesis of Allbutt. The hypertension becomes permanent in late middle life, not in senium but in senescence, as Allbutt says. These patients carry their high blood pressure for many years. They do not die of renal insufficiency, but of intercurrent infections, or of diseased coronary arteries of the heart, or of arterial disease of the brain. The absence of renal insufficiency speaks for the slow progress of the arteriolosclerosis in the kidneys and Loehlein spoke of these cases as nephrocirrhosis arteriolosclerotica lenta.

We have then corresponding to the concept of renal arteriolosclerosis without renal insufficiency, or benign renal sclerosis, a disease, characterized clinically by chronic hypertension without renal insufficiency, and characterized anatomically by arteriosclerosis of the small arteries and arterioles in the kidneys with narrowing of their lumen, and obliteration of some of the glomeruli, without any inflammatory changes in them, and leaving a sufficient number of glomeruli intact to perform the function of the kidneys.

Malignant Renal Sclerosis. With the separation of this large group of chronic hypertension without renal insufficiency, there remains a small group of cases in which after prolonged hypertension renal insufficiency supervenes. These cases correspond to the primary contracted kidney or the genuine contracted kidney of the older clinicians. Their separation from chronic glomerulonephritis was accomplished by Volhard and Fahr. Volhard found that among the cases of chronic hypertension in which renal arteriolosclerosis could be assumed to be present, there were some in which the hypertension was of an extreme degree and in which total renal insufficiency gradually supervened in the same manner as in chronic glomerulonephritis. When Volhard and Fahr examined the kidneys of these cases they found the arteriosclerosis of the small arteries

and the arterioles to be of an extreme degree. The arteries and the arterioles were thickened, with fatty and hyalin degeneration of their walls, in many the lumen was completely closed and very many glomeruli were completely obliterated. The changes found in chronic glomerulonephritis were not found in these cases. Evidently these cases presented an advanced degree of renal arteriolosclerosis. But Volhard and Fahr found more. The arteries and the arterioles in the kidneys showed an inflammation of the intima and necrosis of the vessel wall in an irregular distribution, an arteriolitis and an arteriolonecrosis. In addition, the glomeruli showed small areas of inflammation in an irregular focal distribution. Evidently a focal inflammatory process of the arterioles and glomeruli had been added to the arteriolosclerosis. Volhard and Fahr, therefore, spoke of this form of kidney disease as the combination form. Both, however, dropped this term later. Volhard speaks of this form as the ischemic end stage of arteriolosclerosis, while Fahr calls it malignant renal sclerosis. I have preferred the term renal arteriolosclerosis with renal insufficiency, but the term malignant renal sclerosis really expresses the same thing and is much shorter.

These cases of malignant renal sclerosis or renal arteriolosclerosis with renal insufficiency increase in frequency with the closer acquaintance with this form of kidney disease. Klemperer reported a study of 18 cases at a meeting of the New York Pathologic Society. Fahr assumes that the inflammatory reaction in the vessels and glomeruli is caused by a specific poison, either lead, or syphilis. In his own cases, however, there were many who did not have lead or syphilis as etiologic factors. Loehlein and Herxheimer consider the inflammatory changes as reparative, due to the collapse of some of the glomeruli. Loehlein considers the whole process as an extreme degree of renal arteriolosclerosis and calls this form of kidney disease nephrocirrhosis arteriolosclerotica progressa. Cases of renal arteriolosclerosis with renal insufficiency, in which the inflammatory changes are absent, also occur.

We have then corresponding to the concept of renal arteriolosclerosis with renal insufficiency, or of malignant renal sclerosis a disease which is characterized clinically by hypertension of many years, to which renal insufficiency is gradually added. It is characterized pathologically by an extreme degree of arteriolosclerosis, with the addition in the greater number of cases, of an arteriolitis and an arteriolonecrosis in a focal distribution.

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STUDIES OF SERUM ELECTROLYTES. VI. WATER METABOLISM IN PNEUMONIA.*

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In previous papers[1,2,3] the authors presented data on the distribution of electrolytes in the body during lobar pneumonia. The possibility that the decreased concentration of the total base, chlorid and protein of the serum during the active infection might be due in part to a retention of water in the body and a dilution of the serum has been discussed. The present paper is concerned with our observations of the water metabolism in patients suffering with lobar pneumonia and with a consideration of the factors involved in the calculation of the water balance.

From the beginning, the difference between changes in the water balance and changes in the percentile water content of tissue should be kept clearly in mind. The water balance represents the difference between the total water intake and the total water output, and while this quantity includes the water of oxidation of the foods it does not take into account the water exchange of the tissues when they are metabolized. As it is generally recognized and as the data in this study demonstrate, the diet during the precritical period of pneumonia is inadequate for the metabolic needs of the subject so that it becomes necessary for him to catabolize his own tissues. Associated with the catabolism of tissues there is every reason from studies in inanition, such as those of Benedict and his associates,[4,5] to expect a release of preformed water from the catabolized tissues as well as the formation of water of oxidation from these tissues. If the percentile water content of the remaining tissues be unchanged, then the water derived from the catabolized tissues must be excreted and the water balance will become negative by that amount. It is thus possible to have a negative water balance without change in the percentile water content of the body tissues and likewise, if only part of the water derived from catabolized tissues be excreted, it is also possible to have a negative water balance with an increase in the percentile water content of the remaining tissues.

* Aided by a grant from the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.

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In our studies we have estimated the water balance from data on intake, output and change in weight. For the interpretation of the water balance, however, we have attempted to estimate within limits the water derived from metabolized tissues.

The interpretation of the water metabolism in pneumonia and fever in general has led some to the view that there is water retention in the body and others that there is an actual diminution in the water content of the body. Much of the confusion, especially in the early literature, can be attributed to the various interpretations as to what measures the water metabolism. The workers who demonstrated by means of intake and output records that there was less water in the body during the course of a fever than at its beginning, concerned themselves with changes in what we might regard as the water balance. On the other hand, the investigators who studied such relationships as the ratio of water content to solid content in the blood, tissues, or entire body have been concerned with changes in the percentile water content of the tissues. We shall not attempt to cover the large literature on water metabolism during fever but shall merely point out some of the studies bearing on the water relations of the body during lobar pneumonia.

Leyden,[6] in 1869, first studied the problem of water metabolism in pneumonia. He showed by means of weight studies that there was an increased loss of weight through the skin and lungs during the febrile period. At the time of crisis he observed free sweating and rapid loss of weight. The loss of weight continued even after the crisis when his patients were returning to their normal state, which he attributed to an earlier incomplete excretion of water during the febrile period.

Sandelowsky[7] studied the serum proteins, salt balance, and body weights in 11 cases of pneumonia. He considered the serum protein an index of blood concentration. In 7 cases the body weight either increased slightly during the fever or remained constant, whereas after the crisis the weight fell more or less rapidly. During the febrile period there was generally a decreased concentration of protein, the correlation of which with the increased or constant weight Sandelowsky believed could not be explained otherwise than by an actual retention of water in the serum. In his remaining group of 4 cases there was a continued decrease in weight during the febrile and afebrile periods which Sandelowsky attributed to a loss of body tissues which overcompensated, so far as weight was concerned, for a percentile increase of water in the remaining tissues. According to him, previously healthy individuals who developed a mild pneumonia would have retention of water with increased weight, whereas, severe pneumonia cases in which there was much tissue wasting were apt to have water retention in the remaining tissues with decreased weight.

Schwenkenbecker and Inagaki[8] studied the ratio of water to dry

substance in muscle and pieces of liver obtained from patients who died of acute febrile infections including pneumonia. They found an increase in percentile water content as a result of an absolute diminution of solids. These authors stressed the absence of water retention in the body in acute infections except when heart or kidneys were diseased.

Hutchison[9] found a slight increase in the water content of voluntary muscle in pneumonia and Garratt[10] demonstrated a small increase in the water content of heart muscle. Additional corroborative evidence dealing with increase in percentile water content of tissues should include the observations of Mayer and Schwartz[11] using the Schade elastometer with which they demonstrated moderate degrees of edema in subcutaneous tissues of all of their pneumonia cases; and the recent observations of Soule, Buckman and Darrow[12] on blood volume in fever in which they found that there was an increase in the plasma volume in fever accompanied by an increase in the water held diffusely throughout the body.

Materials and Methods. Our studies were carried out on 7 patients suffering with pneumonia, to 3 of whom large quantities of sodium chlorid were administered. We also report the water balance of two normal subjects who for another purpose were put for forty-eight hours upon the same limited diet which the pneumonia patients received and who during this period were sweated vigorously by light baths.

All of the subjects studied were weighed at seven o'clock each morning to within ± 10 gm. The dry weights of the ingesta and egesta were determined with the exception of the sputum and the blood removed for analysis. The sputum was arbitrarily regarded as containing 5 per cent solids. The blood solids were taken as 20 per cent of the total amount of blood removed, using Gram's average figures.[13] For the details of our methods, the reader is referred to Paper IV of this series.[2]

Calculations and Results. Our method of estimating water balance from our data is indicated in the following equations. Throughout this paper an arbitrary *allowance for maximum error* has been made for each measurement and estimate. The allowance for error is designated in text and tables by the symbol ± and must not be confused with probable error or other statistical function. No conclusions have been drawn from positive or negative balances except where they exceed the allowance for error as computed.

Calculation of Absolute Water Balance. Measured intake (grams):

(1) $$I = \text{food} + \text{beverage} + \text{enema in grams} \pm 2 \text{ per cent.}$$

Measured intake of water (grams):

(2) $$W_i = [\text{water of food estimated from tables (but not the water of oxidation)} + \text{beverage} + \text{enema}] \pm 2 \text{ per cent}$$

Water of oxidation of food intake (grams):

$$W_{ox.i} = (0.413\ P_i + 0.555\ C_i + 1.071\ F_i) \pm 2 \text{ per cent} \tag{3}$$

where P_i, C_i and F_i are the grams of protein, carbohydrate and fat in the intake. The amount of water formed by oxidation is taken from Magnus-Levy's[14] calculations that 100 grams of protein give 41.3 grams of water; 100 grams of carbohydrate give 55.5 grams of water; 100 grams of fat give 107.1 grams of water.
Total water intake (grams):

$$W_{ti} = W_i + W_{ox.i} \tag{4}$$

Measured output (grams):

$$O = (\text{urine} + \text{feces} + \text{sputum} + \text{blood removed}) \pm 2 \text{ per cent} \tag{5}$$

Measured water output (grams):

$$W_o = (W_u + W_{fec} + W_{sp} + W_{bl}) \pm 2 \text{ per cent} \tag{6}$$

Daily change in weight (grams):

$$\triangle Wt = (\text{initial weight} - \text{final weight}) \pm 20 \text{ grams} \tag{7}$$

Weight loss through skin and lungs (grams):

$$-\triangle W_{ts.l.} = -\triangle Wt - (O - I) \tag{8}$$

Weight loss due to excess of CO_2 in grams over O_2 in grams:

$$(CO_2 - O_2) = \frac{Cal_t}{Cal_{L.O_2}} \left(\frac{44.0\ R.Q.}{22.4} - \frac{32}{22.4} \right) \tag{9}$$

where

Cal_t = total metabolism in calories
$Cal_{L.O_2}$ = calories per liter of oxygen consumed
R.Q. = respiratory quotient

None of the quantities (Eq. 9) has been measured in our studies but they may be estimated subject to an allowance for error. Our method has been to estimate the basal metabolism for age and weight from Sage normal standards (Aub and Du Bois[15]) and Meeh's formula, with an addition for fever estimated by the average percentile increase of metabolism per degree increase of temperature from Du Bois' data and an additional 10 per cent during the precritical period for excessive protein destruction.[16] The caloric range we use is from 90 per cent of this value to 1000 calories above this value and doubtless includes the true value. The range taken is given in table. The *R.Q.* is estimated[17] by assuming complete metabolism of the food intake, a total protein metabolism measured by the urinary nitrogen, and the residual calories assumed furnished from body fat. In the table we give the values used for $(CO_2 - O_2)$

with the allowance for error. When the range of values by the above method of computation is less than ± 20 grams we have arbitrarily taken the allowance for error as of this magnitude.

Water loss through skin and lungs, neglecting the solids of the sweat which are assumed to be less than 0.5 per cent of the water loss (grams):

(10) $W_{s.l.} = [-\triangle W_{ts.l.} - (CO_2 - O_2)] \pm$ error. (See table.)

Total water output (grams):

(11) $W_{tt.o.} = (W_o + W_{s.l.}) \pm$ error. (See table.)

Daily water balance:

(12) $W\ Bal = (W_{t.i.} - W_{t.o.}) \pm$ error. (See table.)

The data required for these equations is to be found in part in table and in part in Papers IV and V of this series.

The day on which the crisis occurred is designated as the O day; the days before the crisis as − days; and the days after the crisis as + days.

Our cases may be divided into two groups, the first group (B1, B2, B4 and B5) representing pneumonia patients under the ordinary régime; and the second group (B3, B6 and B7) representing patients receiving unusual treatment. Case B3 was given a high-caloric diet on the first two days of study (−3 and −2 days); and Cases B6 and B7 were given extra salt with their diets during the precritical period.

In the first group of our cases up to the day of crisis the water balance was between −470 and +700 grams including the allowance for error. During the precritical period there was a positive water balance for one day in B2 and B4 respectively. At the time of crisis each of the cases in the group showed a tendency toward increase of the negative water balance. For the most part during the epicritical period the water balance was negative except in B5 where it became positive associated with the development of a large empyema. Thus the water balance in pneumonia patients under the ordinary régime before and after the crisis was predominantly negative, although exceptions occurred in both periods.

In the second group of our cases the water balance was positive during the first day of study in B3, it was questionably positive during the precritical period in B6, and was definitely positive during the precritical period in B7. The tendency toward water retention was very prominent in B7 who had great gain in weight and eventually visible edema. B6 showed the same tendency although it was less marked. After the crisis at a time when the salt intake was decreased, the water balance became negative. Thus the water balance tended to become positive before the crisis in our pneumonia patients who received extra quantities of salt precritically, whereas, after the crisis, when the salt intake was decreased, it became negative.

DATA ENTERING INTO WATER BALANCE.

Case No.	Day from crisis.	Caloric intake.	Estimated caloric requirement, $Cal_{t.}$	Measured water intake, $W_{i.}$	Water of oxidation of food, $W_{ox.i}$	Total water intake, $W_{ti.}$	Weight loss, skin-lungs, $-\triangle Wt_{s.l.}$	(CO_2-O_2).	Total water output, $W_{t.o.}$	Water balance, WBal.	Estimate of water from body tissues, $W_{tis.}$	Direction of	
												Water balance, WBal.	Relative water balance, $WBal_{rel.}$
B1	−1	755	2000–3230	3999	94	4093	3040	46 ± 20	4382 ± 68	− 289 ± 150	509 ± 77	−	?
	0	799	1850–3060	3460	99	3559	2744	64 ± 20	3892 ± 64	− 333 ± 135	539 ± 75	−	?
	+1	786	1440–2595	2537	97	2634	2714	60 ± 20	3953 ± 66	−1319 ± 119	510 ± 73	−	−
B2	−3	1067	2140–3380	3627	126	3753	2196	71 ± 20	3537 ± 68	+ 216 ± 144	587 ± 78	+	+
B3	−3	2733	3240–4600	3928	320	4248	2436	117 ± 21	3932 ± 73	+ 316 ± 158	412 ± 85	+	+
	−2	1412	3240–4600	5090	163	5253	2174	52 ± 20	5759 ± 113	− 506 ± 218	737 ± 85	−	?
	−1	33	2920–4250	3546	4	3550	2197	20 ± 20	4702 ± 91	−1152 ± 162	1010 ± 83	−	?
	0	391	3160–4510	4523	49	4572	4276	20 ± 40	5624 ± 67	−1052 ± 158	886 ± 85	−	?
	+1	1160	2510–3800	3763	145	3908	2584	83 ± 20	4411 ± 78	− 503 ± 156	887 ± 80	−	+
	+2	1227	2510–3800	3422	150	3572	2080	68 ± 20	4108 ± 82	− 536 ± 154	654 ± 80	−	?
	+3	1117	2510–3800	5115	136	5251	2382	57 ± 20	6409 ± 122	−1158 ± 227	750 ± 80	−	−
	+4	1500	2050–3280	3904	184	4088	2274	80 ± 20	5117 ± 99	−1029 ± 181	485 ± 77	−	−
	+5	1002	2050–3280	3441	126	3567	1829	80 ± 20	4061 ± 86	− 494 ± 158	597 ± 77	−	?
	+6	1060	2050–3280	2775	134	2909	1997	80 ± 20	4354 ± 89	−1445 ± 148	509 ± 77	−	−
	+7	555	2050–3280	2906	70	2976	1690	58 ± 20	3551 ± 78	− 575 ± 137	599 ± 77	−	?
B4	−2	800	2410–3680	4525	101	4626	3223	63 ± 20	4619 ± 69	+ 7 ± 162	838 ± 79	?	+
	−1	939	2340–3600	6035	117	6152	3223	77 ± 20	5663 ± 90	+ 489 ± 213	825 ± 79	+	+
	0	861	2210–3480	4022	107	4129	3086	62 ± 20	6067 ± 101	−1938 ± 184	820 ± 78	−	−
	+1	798	2210–3480	3202	99	3301	2554	50 ± 20	5118 ± 106	−1817 ± 172	706 ± 77	−	−
	+2	698	2040–3270	2183	88	2271	1909	58 ± 20	3301 ± 69	−1030 ± 115	667 ± 77	−	−
	+3	936	1800–3000	4346	116	4462	1689	63 ± 20	4239 ± 92	+ 223 ± 181	571 ± 75	+	+
	+4	1014	1630–2810	3425	127	3552	1631	75 ± 20	4590 ± 101	−1038 ± 173	395 ± 74	−	−
	+5	943	1630–2810	3231	119	3350	1499	75 ± 20	3845 ± 88	− 495 ± 155	440 ± 74	−	?
	+6	1508	1630–2810	3540	188	3728	2029	129 ± 35	3479 ± 87	+ 249 ± 162	294 ± 74	+	+
	+7	2707	1630–2810	3104	328	3432	717	112 ± 30	3108 ± 100	+ 324 ± 169	47 ± 74	+	+
	+8	1924	1630–2810	2894	235	3129	927	93 ± 25	3765 ± 104	− 636 ± 167	295 ± 74	−	?

	+7	2707	1630–2810	3104	328	3432	717	112 ± 30	3108 ± 100	+ 324 ± 169	47 ± 74	+	+
	+8	1924	1630–2810	2894	235	3129	927	93 ± 25	3765 ± 104	− 636 ± 167	295 ± 74	−	?
B5	−3	890	1380–2540	3193	111	3304	1774	59 ± 20	3457 ± 75	− 153 ± 141	291 ± 72	−	?
	−2	773	1380–2540	3039	96	3135	924	59 ± 20	3371 ± 90	− 236 ± 153	350 ± 72	−	?
	−1	782	1380–2540	2402	97	2499	813	50 ± 20	2527 ± 75	− 28 ± 125	291 ± 72	?	+
	0	840	1380–2540	3543	105	3448	896	59 ± 20	4287 ± 109	− 639 ± 182	332 ± 72	−	−
	+1	707	1030–2140	2504	89	2593	941	54 ± 20	2929 ± 81	− 336 ± 133	215 ± 70	−	?
	+2	1361	1030–2140	2728	171	2899	649	117 ± 41	2151 ± 93	+ 748 ± 151	38 ± 70	+	+
	+3	1557	1030–2140	2589	190	2779	825	74 ± 26	2281 ± 77	+ 498 ± 133	35 ± 77	+	+
B6	−5	1063	1860–3070	3763	132	3895	2516	64 ± 20	4320 ± 77	− 425 ± 155	419 ± 76	−	?
	−4	1303	1760–2960	4346	162	4508	2085	81 ± 21	3670 ± 74	+ 838 ± 164	378 ± 75	+	+
	−3	1340	1640–2820	4199	166	4365	1970	76 ± 20	4225 ± 87	+ 140 ± 174	242 ± 74	?	+
	−2	1369	1640–2820	3567	169	3736	1822	93 ± 25	3890 ± 88	− 154 ± 162	282 ± 74	?	?
	−1	1340	1640–2820	3795	165	3960	1856	85 ± 23	3942 ± 86	+ 18 ± 165	241 ± 74	?	+
	0	1299	1640–2820	3627	161	3788	1758	85 ± 23	4107 ± 92	− 319 ± 167	228 ± 74	−	?
	+1	1270	1540–2720	3345	159	3504	1815	81 ± 22	3770 ± 83	− 266 ± 153	204 ± 73	−	?
	+2	1370	1540–2720	3180	169	3349	2064	81 ± 22	3894 ± 80	− 545 ± 147	190 ± 73	−	−
	+3	1187	1540–2720	2602	146	2748	1822	72 ± 20	3534 ± 76	− 786 ± 131	276 ± 73	−	+
	+4	1090	1540–2720	2233	134	2367	1878	64 ± 20	3080 ± 65	− 713 ± 113	228 ± 73	−	−
B7	−6	1030	2180–3410	2825	128	2953	1703	49 ± 20	2937 ± 66	+ 16 ± 125	304 ± 78	?	+
	−5	1050	2060–3290	4013	129	4142	2113	47 ± 20	4082 ± 80	+ 60 ± 163	307 ± 77	?	+
	−4	1207	1860–3070	4241	149	4390	1278	79 ± 20	3426 ± 85	+ 964 ± 173	528 ± 76	+	+
	−3	1137	1860–3070	4600	141	4741	1658	64 ± 20	4528 ± 99	+ 213 ± 194	406 ± 76	+	+
	−2	1137	1860–3070	3871	140	4011	795	73 ± 20	2769 ± 81	+1242 ± 161	297 ± 81	+	+
	−1	1137	1860–3070	3996	140	4136	989	73 ± 20	2468 ± 71	+1668 ± 154	411 ± 76	+	+
	0	1117	1770–2970	3558	137	3695	872	51 ± 20	1958 ± 68	+1737 ± 137	199 ± 75	+	+
	+1	790	1770–2970	2441	97	2538	1018	41 ± 20	2159 ± 64	+ 379 ± 115	293 ± 75	+	+
	+2	595	1670–2860	1547	72	1619	802	31 ± 20	1933 ± 63	− 314 ± 95	316 ± 74	−	?
	+3	910	1670–2860	1869	112	1981	868	39 ± 20	2037 ± 64	− 56 ± 103	232 ± 74	?	?
B8	1	830	2100–3340	2988	104	3092	2502	147 ± 34	3789 ± 83	− 697 ± 145	404 ± 80	−	−
	2	850	2100–3340	2607	107	2714	2092	135 ± 31	3060 ± 73	− 346 ± 127	409 ± 80	−	?
B9	1	765	2260–3520	3319	95	3414	2079	144 ± 31	4674 ± 106	−1260 ± 174	380 ± 80	−	−
	2	800	2260–3520	2847	100	2947	2034	144 ± 31	3634 ± 86	− 687 ± 145	403 ± 78	−	−

In two normal subjects, B8 and B9 who were fed for forty-eight hours on a low diet comparable to that received by the pneumonia patients under the ordinary régime, the water balances were negative on both days in both subjects. This is the finding to be expected in the early stages of inanition when the glycogen stores in the body are being reduced.

Since all of our patients partook of a diet which was calorically inadequate and exhibited negative nitrogen balances, positive water balances, when they occur indicate without question an increase of the percentile water content of at least certain tissues. The interpretation of the water balances is, however, quite difficult since the water derived from the catabolized tissues should be considered. In the table is given our approximate estimates of the amount of water released from catabolized tissues made on the assumption that the negative nitrogen balance was derived from tissues containing 3.4 per cent of nitrogen and 76 per cent of water and the remaining calories from fat containing 10 per cent of water.‡ Insofar as these estimates be correct they would signify that the release and formation of water associated with the marked tissue catabolism was sufficient and often more than sufficient to account for the negative water balance frequently observed during the precritical period of lobar pneumonia.

Loss of Water by Skin and Lungs. The loss of water by way of the skin and lungs was greatly increased throughout the period of study, being most marked at the time of the crisis. At the time of the maximal loss of water from skin and lungs the urinary water was usually diminished. It is noteworthy that in Case B7 in whom there was salt retention and visible edema there was decreased loss of water through skin and lungs. The loss of water through skin and lungs in Case B5 was of the same order of magnitude, but B5 was a boy 26 kilos in weight as compared with B7 approximately 60 kilos in weight.

Water Intake. Our patients took large quantities of water during the febrile period and especially near the crisis. In the control subjects to whom water was deliberately forced to the point of discomfort, the water intake did not reach the amount which was

‡ The figures for the estimates of the water derived from body tissues have been obtained by use of the following equations:

$$W_{tis} = W_{ox.tis.} + W_{pref.}$$

where $W_{ox.tis.}$ is the water of oxidation of the tissues and $W_{pref.}$ is the preformed water held with the tissues.

$$W_{ox.tis.} = 2.58(N_u + N_f - N_i) + 1.071\ F_b$$

N_u = Nitrogen output in urine (grams)

N_f = Nitrogen output in feces (grams)

N_i = protein intake (grams) ÷ 6.25

F_b = estimated consumption of body fat from Cal_t

$$W_{pref.} = \frac{0.76\ (N_u + N_f - N_i)}{0.034} + 0.10\ F_b$$

taken easily by our pneumonia patients. This we believe to be correlated with the increased percentile content of water of certain tissues in the pre-critical period. We interpret it as evidence of a demand in at least certain tissues for water.

Discussion. General discussions of water balance in health and disease are to be found in reviews by Rowntree[18] and by Marriott[19].

In attempting any correlation between the water metabolism and the serum changes which we observed in patients suffering with lobar pneumonia, it has been necessary to consider the relation between the total amount of water available for excretion in the organism and the total amount of water excreted. In the water available for excretion we would include the water entering through the ingestion of liquids and food, the water of oxidation, and the water released in the metabolism of body tissues. The total amount of water excreted consists of the water loss through the urine, feces, sweat, breath, sputum, blood removed for analyses and any other secretions leaving the body. The difference between the water available for excretion and the water actually excreted might be termed a *relative water balance* and thus could be regarded as a measure of the percentile water content per unit of body tissues. A relative water balance would thus differ from the water balance, as ordinarily used, in the fact that the water balance does not take into account the water released and formed by oxidation in the metabolism of the tissues. There is reason to believe that this quantity may be considerable where there is tissue destruction although our data will not enable us to estimate it with any certainty. Nevertheless, in spite of this uncertainty it would seem to us desirable to consider it with appropriate allowances for error.

When the water released from catabolized tissues is taken into account, there appears to be an increase in the percentile water content of at least certain tissues even on those precritical days when the water balance was negative. Obviously on the days when the water balance was positive, the percentile water content of the tissue was without doubt increased even though the water released from catabolized tissues be entirely neglected. At the time of crisis the negative water balance reached a magnitude which exceeded the amount we estimated had been released from the tissue catabolism. Thus our studies, as well as others in the literature, seem to indicate that during the later precritical period in pneumonia there is increase in percentile water content of at least certain tissues coincident with variable water balance. As to the time at which this change begins, evidence is lacking because observations early in the disease have not been obtained.

The tendency to an increase in the percentile water content of the body tissues during the precritical period of lobar pneumonia is in the same direction necessary to explain a dilution effect in the serum. However, our approximations would indicate that the

magnitude is not sufficiently large to account for the serum changes we observed. The decreased concentration in the serum electrolytes must, therefore, be attributed in part to other factors leading to a redistribution of water and electrolytes between the serum and the tissues.

Summary. The water balance has been studied for a few days before and after the crisis in a series of 4 cases of lobar pneumonia on the ordinary but measured intake and in 3 additional cases, 2 of whom received large amounts of sodium chloride by mouth and the other a high-caloric diet for two days. In the patients under the ordinary régime daily negative water balances were the usual findings before the crisis. The patients receiving large doses of sodium chloride exhibited either a decrease of the negative water balance or a positive water balance.

Our studies of the water balance furnish no evidence suggesting a percentile decrease in the water content of the body tissues before the crisis; on the contrary, they do furnish definite evidence of a percentile increase of the water content of the tissues on several precritical days.

The difference between changes in water balance and changes in the percentile content of water in tissue has been discussed.

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A STUDY OF HEMOPHILUS INFLUENZÆ.*

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In September, 1926, the problem was started of grouping serologically Hemophilus influenzæ by means of agglutination and precipitin reactions, and of testing the virulence of these strains, thereby to determine if there was any correlation between serologic grouping and strain virulence.

Preliminary Experiments. Twenty-eight strains of Hemophilus influenzæ were isolated from cultures of the pharynx, sputum, pleural fluids and one spinal fluid. The virulence of these microörganisms varied when injected into the peritoneal cavity of mice. In eight strains, 1 billion microörganisms killed the animals within eighteen hours, and in two strains the fatal dose in this time was ½ billion microörganisms. All these strains were considered virulent. The eighteen other strains, in which 2 billion of the microörganisms did not kill mice after seventy-two hours were considered avirulent. Immune monovalent sera were prepared in rabbits for eight of these virulent strains.

In January, 1927, a strain of Hemophilus influenzæ was isolated from the sputum of a patient suffering with acute influenza, on the third day of the disease. One-eighth of a billion microörganisms of this strain, designated as the Hammett strain, killed mice within eight hours. Because this strain appeared unusually virulent for mice, it was tested in rabbits. One-quarter of a billion living microörganisms of this strain injected intravenously, killed the rabbit over night, and a pure culture of it was recovered from the lungs, peritoneal exudate, and the heart blood.

Experimental Work. A series of experiments was then started to test whether the pathogenic factor of this strain was a toxic agent, which might be demonstrated in the filtrates of cultures. Parallel experiments were conducted with other strains of Hemophilus influenzæ, isolated from patients in the Philadelphia General Hospital. This work was divided in the following manner:

* A Thesis in Bacteriology. Presented to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(*a*) Cultural experiments and virulence tests with twenty-three strains of Hemophilus influenzæ isolated from human sources.

(*b*) Experiments with culture filtrates of Hemophilus influenzæ.

(*c*) Rabbit experiments.

(*d*) Biologic studies on Hemophilus influenzæ.

(*e*) Serologic reactions with immune serum.

(*f*) Therapeutic tests of Hemophilus influenzæ (Hammett strain) immune serum.

(*a*) **Cultural Experiments and Virulence Tests with Twenty-three Strains of Hemophilus Influenzæ.** 1. *Preservation of Stock Cultures of Hemophilus influenzæ.* Because of the observation of workers[1] that Hemophilus influenzæ quickly loses its virulence when kept on artificial media, a method of preserving the virulence of stock cultures was sought. The culture medium employed in this study was brown blood broth, that is, infusion broth of pH 7.6 to 7.8 to which approximately 7 per cent by volume of sterile defibrinated blood was added. This was then heated until the blood became a rich brown color. The medium was tubed and incubated at 37.5° C. to test its sterility before use.

When cultures were first isolated from patients or from animals, transplants were made every three or four days, but as the cultures became adapted to the medium, transfers were necessary only every three weeks. At the time of transplanting, the cultures were also tested for purity by plating on brown blood agar. Those used for experimental work were always kept in the brown blood-broth medium, at room temperature (18° to 20° C.). It was found, in the course of this study, that cultures of Hemophilus influenzæ though virulent as long as grown in brown blood broth, when transplanted to a solid medium for four or five generations, became avirulent. When stock cultures were kept at ice-box temperature, loss of virulence was more rapid than at room temperature. In the two years that the Hammett strain has been under observation, it has lost little of its original virulence. The cultures of the Hammett strain reclaimed after animal passage, and also strains from other sources, have all been maintained in the same manner and have remained virulent.

Thus, the virulence of a culture of Hemophilus influenzæ has been maintained over a period of two years, all strains studied being cultivated and stored in a fluid medium, that is, brown blood broth, at room temperature (18° to 20° C.). It appears that the important points in this method of cultivation are the composition of the medium and the temperature at which the cultures are kept.

2. *Virulence Tests.* In testing virulence, 0.2 cc. of a brown blood broth culture of Hemophilus influenzæ was streaked on a brown blood-agar plate and incubated at 37.5° C. After eighteen hours the growth was washed from the plate with infusion broth, since it was found that an exposure of ten minutes to physiologic saline solution destroyed the virulence. The suspension was centrifuged

at low speed for a half minute to remove agar particles, and diluted to contain 1 billion microörganisms per cubic centimeter using infusion broth as the diluent. It was then injected intraperitoneally into the mouse. Estimation of the virulence of a strain was based upon the numbers of microörganisms and the time required to cause the death of the mouse. Of the twenty-three strains studied, thirteen were virulent and ten were avirulent.

(*b*) **Experiments with Culture Filtrates of Hemophilus Influenzæ.** 1. *Preparation of Filtrates.* Filtrates were obtained of the brown blood-broth cultures after growing the bacteria for eighteen hours at 37.5° C. After centrifuging the culture to throw down the heavy particles of the medium, the supernatant fluid was filtered through a Grade N. Berkefeld filter. For the Hammett strain, it was found that this filtrate would kill mice within eighteen hours when 2 cc. was injected intraperitoneally, and rabbits when 3 cc. was injected intravenously. Filtrates from the other strains had to be used in larger volumes to produce corresponding effects.

2. *Skin Reactions with the Culture Filtrate of the Hammett Strain.* The culture filtrate of the Hammett strain prepared as described above in dilutions of from 1 to 100 to 1 to 7000 for skin tests upon individuals volunteering for the study. Control tests were made with filtered brown blood broth and normal horse serum similarly diluted. Sixty individuals were tested using 0.1 cc. of the dilutions of filtrate injected intradermally. The results were read after six and eighteen hours. After forty-eight hours the local reactions had faded materially. The typical reactions consisted of an erythema or a pink papule around the point of injection, and at times the erythema was surrounded with a blanched area. An erythematous reaction of less than 5 mm. in diameter was regarded as negative. Table I shows the results of these tests, the measurements of the local erythema being recorded in millimeters.

In the first group of 60 nonfebrile patients in the hospital wards, 42 gave positive skin reactions, the remaining were negative, or gave positive reactions in the control. Several individuals who gave negative results gave histories of exposure to influenza patients in the 1918 epidemic without contracting the disease at that time. Others had had very severe attacks of influenza in 1918 and recovered. One of these individuals had had a typical attack of influenza in the epidemic of 1889–1890 and though thoroughly exposed in the epidemic of 1918 did not contract the disease. In the second group of 75 normal volunteers, representing students, interns, nurses and laboratory workers, 51 gave positive and 24 negative skin reactions, or approximately 68 per cent reacted positively.

The results of the foregoing experiments show: (1) In virulent cultures of Hemophilus influenzæ there appears to be a toxic agent capable of causing death of white mice when injected intraperitoneally. (2) This toxic agent is not found in filtrates of avirulent

strains. (3) Culture filtrates of virulent strains of Hemophilus influenzæ produced skin reactions in 68 per cent of humans when employed in dilutions up to 1 to 7000. This test seems to be analogous to the Schick or Dick test and appears to be of such a nature that it may be of value in determining susceptibility to infection with Hemophilus influenzæ, and should be further investigated.

TABLE I.—RESULTS OF SKIN TESTS ON HUMANS, PERFORMED WITH FILTRATE OF CULTURES OF HEMOPHILUS INFLUENZÆ (HAMMETT STRAIN), THE READINGS BEING RECORDED IN MILLIMETERS.

Patient.	1 to 100.	1 to 1000.	1 to 2000.	1 to 3000.	1 to 4000.	1 to 5000.	1 to 6000.	1 to 7000.	Control.*
1	20 x 20	20 x 18	8 x 10	7 x 7	–	–	–	–	–
2	18 x 14	15 x 15	15 x 15	12 x 10	10 x 10	7 x 5	–	–	–
3	22 x 15	18 x 20	11 x 12	10 x 10	5 x 7	–	–	–	–
4	18 x 25	18 x 20	20 x 20	20 x 15	10 x 10	–	–	–	–
5	23 x 22	20 x 18	8 x 7	9 x 10	10 x 10	5 x 5	–	–	–
6	19 x 22	16 x 26	14 x 22	14 x 20	10 x 10	10 x 10	–	–	–
7	30 x 25	26 x 22	14 x 26	11 x 5	9 x 6	5 x 6	5 x 5	–	–
8	17 x 20	14 x 15	11 x 22	10 x 15	9 x 5	–	–	–	–
9	14 x 11	13 x 10	10 x 11	5 x 5	–	–	–	–	–
10	...	19 x 24	17 x 18	16 x 16	16 x 15	6 x 6	–	–	–
11	...	18 x 20	11 x 11	9 x 10	9 x 10	7 x 6	–	–	–
12	...	22 x 22	16 x 14	16 x 15	12 x 11	5 x 5	–	–	–
13	...	26 x 22	20 x 18	15 x 16	12 x 12	10 x 10	–	–	–
14	...	18 x 20	15 x 19	15 x 19	15 x 17	10 x 10	–	–	–
15	...	10 x 15	8 x 8	8 x 7	7 x 6	8 x 6	5 x 6	–	–
16	...	20 x 22	19 x 19	16 x 17	11 x 10	11 x 5	5 x 5	–	–
17	...	17 x 22	17 x 15	16 x 10	14 x 14	10 x 10	–	–	–
18	...	17 x 17	15 x 12	15 x 12	15 x 10	5 x 5	–	–	–
19	...	16 x 18	11 x 14	10 x 13	8 x 6	3 x 3	–	–	–
20	...	14 x 15	...	...	...	14 x 13	12 x 14	9 x 7	–
21	...	10 x 14	...	...	...	11 x 9	7 x 7	–	–
22	...	12 x 10	...	...	...	10 x 10	9 x 10	7 x 6	–
23	...	12 x 16	...	...	...	14 x 14	14 x 16	9 x 7	–
24	...	10 x 10	...	...	...	9 x 9	10 x 7	6 x 6	–
25	...	...	...	...	...	15 x 16	10 x 11	6 x 6	–
26	...	...	...	...	...	10 x 8	8 x 6	4 x 5	–
27	...	...	...	...	...	11 x 12	10 x 7	4 x 9	–
28	...	...	...	...	...	14 x 12	11 x 9	7 x 4	–
29	...	...	...	...	...	9 x 10	6 x 7	5 x 8	–
30	...	...	...	...	...	25 x 27	14 x 11	9 x 4	–
31	...	...	...	...	...	11 x 14	9 x 6	4 x 4	–
32	...	...	...	...	...	10 x 8	11 x 8	8 x 5	–
33	...	...	...	...	...	13 x 12	10 x 9	8 x 6	–
34	...	...	...	...	...	16 x 18	12 x 12	9 x 9	–
35	...	...	...	...	...	8 x 8	6 x 8	4 x 4	–
36	...	...	...	...	...	18 x 20	16 x 14	12 x 12	–
37	...	...	...	...	...	14 x 16	8 x 8	4 x 6	–
38	...	...	...	...	...	20 x 20	20 x 16	12 x 16	–
39	...	...	...	...	...	10 x 12	10 x 10	6 x 4	–
40	...	...	...	...	...	8 x 10	8 x 6	4 x 4	–
41	...	...	...	...	...	22 x 18	12 x 12	6 x 6	–
42	...	...	...	...	...	24 x 20	20 x 16	12 x 14	–

The figures at the top of the chart, that is, 1 to 100, 1 to 1000, 1 to 2000 and so forth, represent the dilution of the filtrate used in performing the tests.

* Control, uninoculated filtered brown blood broth and normal horse serum.

(*c*) **Experiments on Rabbits.** As mentioned previously, experiments were carried out on rabbits with Hemophilus influenzæ (Hammett strain). Twenty-three animals were used, 8 for animal passages of the Hammett strain, 7 for culture filtrate injections, 6 for exposure in testing contact infection of animals. Two were used for the implantation in the abdominal cavity of sealed collodion sacs containing culture or filtrate of Hemophilus influenzæ.

1. *Effects of Intravenous Injection.*

Protocols. RABBIT 1. Weight, 2100 gm. Injected with 5 cc. of the supernatant fluid from a centrifugated eighteen-hour culture, of the Hammett strain. The next day the animal was ill; on the fourth day dull and listless; on the fifth day it developed paralysis of the hind legs, diarrhea, and purulent conjunctivitis; on the eighth day the paralysis was very marked, accompanied by spasmodic movements, and the animal died several hours later.

Necropsy. The pleural cavity contained pus. There was an acute purulent pericarditis. The smaller bronchial tubes were filled with pus. The lungs had many small pin-point hemorrhages. There was an acute purulent conjunctivitis. The intestines were distended, the liver was dark and friable, and the kidneys were very pale.

Pure cultures of the microörganisms were recovered from the conjunctiva, from the bronchii of both lungs, from the pleural cavity and from the heart blood.

RABBITS 2 and 3. Weight, 2520 and 2780 gm. Injected with 1 and 2 billion respectively of living microörganisms (Hammett strain). The next morning, both rabbits were dead.

Necropsy. The lungs were hemorrhagic with serous exudate into the plural sac, the heart was pale and there were subcutaneous hemorrhages. The lower lobes of the lungs of both animals were more inflamed than the upper lobes. Hemophilus influenzæ was recovered from the lower lobes of the lungs of both animals.

RABBIT 4. Weight, 3040 gm. Injected intravenously with $\frac{1}{8}$ billion living microörganisms. The next day the animal was quiet and listless. On the second day the animal developed bloody diarrhea and died. Pure cultures of Hemophilus influenzæ were recovered from both lungs and the heart blood.

The foregoing experiments with Rabbits 1 to 4 inclusive show the pathogenicity of the Hammett strain for rabbits. One billion living organisms injected intravenously, killed in eighteen hours. Amounts as little as $\frac{1}{8}$ billion proved fatal to rabbits within forty-eight hours. Acute inflammation of the lungs was produced with pin-point hemorrhages, such as is frequently seen in humans dying of influenza. Acute dilatation of the heart at times accompanied by a purulent pericarditis was noted commonly. A serous exudate was constant in the pleural sacs, and Hemophilus influenzæ was readily recovered in cultures from the heart blood and lungs.

2. *Effects of Subcutaneous Doses.*

Protocols. RABBIT 5. Weight, 2375 gm. Injected subcutaneously with 1 billion living microörganisms and intravenously with 1 cc. of culture filtrate (Hammett strain). The animal died on the third day.

Necropsy. The lungs and peritoneal cavity contained a serous exudate. The lungs showed pin-point hemorrhages. One side of the left lung was completely hemorrhagic. The heart was enlarged and there was pus in the pericardial sac. Pure cultures of Hemophilus influenzæ were obtained from the peritoneal cavity, from the lungs, heart blood and liver.

RABBIT 6. Weight, 2640 gm. Injected subcutaneously with $\frac{1}{4}$ billion living microörganisms of the Hammett strain. Two days later a swelling developed at the point of inoculation. The next day the swelling extended over approximately four square inches of the abdomen. On the fourth day the swollen area opened at the point of inoculation. A small incision was made and cultures taken. These showed pure cultures of Hemophilus influenzæ. By the eighth day the area of infection was extending and by the tenth day the abscess had broken down and a thick, yellow ropy pus exuded. On the fourteenth day the opposite side of the abscess was opened and allowed to drain. On the twenty-fourth day a pure culture of Hemophilus influenzæ was obtained from the wound. In this animal a purulent ulcerating lesion from which Hemophilus influenzæ could be cultured at will persisted until the death of the animal, eight months later. This experiment indicates that the Hemophilus influenzæ organism when injected subcutaneously is not as rapidly fatal as when injected intravenously. Rabbit 6 was used for subsequent experiments.

3. *Results of Experiments for Immunization.*

Protocols. RABBIT 7. Weight, 2200 gm. Animal received subcutaneously $\frac{1}{4}$ billion killed organisms of the Hammett strain on the first, third, fifth and twenty-third days. Injections were not made between the fifth and twenty-third days because of loss of weight of the animal. On the twenty-fifth day $\frac{1}{2}$ billion killed organisms were injected subcutaneously. On the thirty-seventh day $\frac{1}{4}$ billion living organisms were injected subcutaneously. The agglutinin titer of the serum taken just prior to the injection of the living organisms on the thirty-seventh day was 1 to 160. The animal died eighteen days after receiving living organisms. It was ailing for several days with a small lump at the point of inoculation.

Necropsy. The lungs were hemorrhagic with dark pin-point hemorrhages throughout. A serous exudate was present in the pleural cavity, and the heart was much enlarged. Subcutaneous capillary hemorrhages were also present. Pure cultures of Hemophilus influenzæ were recovered from the pus of the point of inoculation, from the lungs, the heart blood and the peritoneal exudate.

RABBIT 8. Weight, 3140 gm. Animal received subcutaneously $\frac{1}{4}$ billion killed organisms of the Hammett strain on the first and third days, and $\frac{1}{2}$ billion killed organisms on the sixth, eighth, tenth and twelfth days. On the fourteenth, eighteenth and twenty-second days, $\frac{1}{16}$ billion living organisms were injected subcutaneously, and $\frac{1}{4}$ billion on the twenty-fourth and thirty-first days. The next day the agglutinin titer of the serum was 1 to 320. The animal developed an abscess at the point of inoculation of the living cultures and was used for subsequent contact experiments. (See Section Four.) The rabbit died after sixty-eight days, presenting throughout this period an abscess at the point of inoculation. No autopsy was performed.

Attempts at immunization with the Hammett strain failed, apparently because of the extreme virulence of this strain. The animals lost weight and when inoculated with living organisms, even following previous inoculations with killed organisms, became infected, and finally death ensued.

4. *Infection of Normal Rabbits Through Exposure to Infected Animals.* Normal rabbits were placed in cages with rabbits previously infected with Hemophilus influenzæ, to determine if spontaneous infection would occur in normal rabbits as a result of contact. By referring to Section three it will be noted that Rabbits 6 and 8 had as a result of experimentation developed chronic abscesses and hence were utilized in this phase of the work to determine if through contact with these rabbits normal rabbits might become infected. The procedure and the results of experiments were as follows:

RABBIT 9. A normal rabbit was placed in a cage with Rabbit 6. Two days latter Rabbit 9 was listless and died nine days later.

Necropsy. The lungs were hemorrhagic with emphysemic patches at the edges. The small bronchi were filled with pus. The heart was enlarged and there was abundant exudate in the peritoneal cavity. Hemophilus influenzæ was recovered from the peritoneal fluid, heart blood and lungs.

As a control, Rabbit 10, a normal rabbit was exposed to Rabbit 13 which had previously received 2 cc. of culture filtrate intravenously to see whether a normal rabbit would become infected from a rabbit receiving filtrate. After five days, no infection developed, in either rabbit. Rabbit 10 was then placed in a cage with infected Rabbit 6 and the result of this experiment was as follows.

RABBIT 10. A normal rabbit was placed in a cage with Rabbit 6. The animal appeared to be ill after two days and died after eleven days.

Necropsy. The lower lobes of the lungs were hemorrhagic and the upper lobes contained pin-point hemorrhages throughout. Hemophilus influenzæ was recovered from the heart blood, and the lungs.

RABBIT 11. A normal rabbit was placed in a cage with Rabbit 6. Rabbit 11 died in ten days. At autopsy, it showed a serous pleural exudate with inflamed and hemorrhagic lungs. Hemophilus influenzæ was recovered from the heart blood, lungs and pleural exudate.

The above experiments show that infection may be transmitted by contact when normal rabbits are exposed in the same cage with infected rabbits, the infection appearing in two days and death occurring within about ten days.

5. *Infection Occurring in Rabbits First Inoculated with a Sublethal Injection of Filtrate and then Exposed to Infected Rabbits with Open Lesions.* Since the experiments in Section Four shows that normal rabbits become infected when brought in contact with rabbits previously infected with Hemophilus influenzæ and having open lesions, experiments were performed to determine if rabbits previously injected with culture filtrate would when brought in contact with infected rabbits, become infected. The procedure and results were as follows:

RABBIT 12. A normal rabbit after receiving 5 cc. of culture filtrate of the Hammett strain subcutaneously was placed immediately in a cage with infected Rabbit 8.*

* As will be shown later, 3 cc. of culture filtrate of the Hammett strain injected intravenously killed in eighteen hours. However, it was found that rabbits withstood larger injections of culture filtrate subcutaneously without succumbing.

After four days of this contact, the animal developed an abscess behind the ear, from which Hemophilus influenzæ was recovered in pure culture. The animal died on the eighth day after exposure. At autopsy, the lungs were hemorrhagic with small patches of emphysema and the heart was enlarged. Hemophilus influenzæ was recovered from the abscess behind the ear, the lungs and heart blood.

RABBIT 13. Received 2 cc. of culture filtrate intravenously and was placed with Rabbit 8. He developed a purulent conjunctivitis and died on the fifth day. An autopsy was performed and Hemophilus influenzæ was recovered from the conjunctivæ, lungs and pleural exudate.

RABBIT 14. The animal received 2 cc. of filtrate intravenously and was placed in a cage with infected Rabbit 6. After two days he was ill; death occurring on the seventh day. At autopsy, Hemophilus influenzæ was recovered from the lungs, heart blood and pleural exudate.

The above experiments show that while normal rabbits exposed to rabbits infected with Hemophilus influenzæ, became infected and died within ten days (Experiments 9 to 12 inclusively), that rabbits which had received a sublethal dose of filtrate became infected and died in approximately seven days. Since the culture filtrates contain no Hemophilus influenzæ, the indication is that these bacteria were acquired by contact infection.

6. *Rabbits Receiving Lethal Doses of Culture Filtrate.* The lethal dose of filtrate of the Hammett strain was determined as follows. Three rabbits were injected with culture filtrate of this strain using varying doses.

RABBIT 15. Weight, 2150 gm. Injected intravenously with 2 cc. of culture filtrate (Hammett strain). The animal survived.

RABBIT 16. Weight, 2420 gm. Injected intravenously with 3 cc. of culture filtrate (Hammett strain).

RABBIT 17. Weight, 2415 gm. Injected intravenously with 5 cc. of culture filtrate (Hammett strain).

RABBITS 16 and 17. These died the day following the injections.

Necropsy. The lungs showed pin-point hemorrhages with a red serous exudate in the pleural cavity, a picture similar to the lungs of rabbits having had injections of living Hemophilus influenzæ organisms. The heart and kidneys were pale, the liver soft and friable. All cultures from organs of these rabbits were negative for Hemophilus influenzæ.

Therefore, since 2 cc. of culture filtrate did not kill and 3- and 5-cc. doses did kill when injected intravenously into rabbits, it can be concluded that 3 cc. was the M.L.D. of culture filtrate when injected intravenously.

7. *Immunization of Rabbits with Culture Filtrates of the Hammett Strain.* Three rabbits (18, 19 and 20) were immunized to the culture filtrate of the Hammett strain, giving sublethal doses at first, and increasing these doses, by giving three injections subcutaneously resting four days, and following with four courses of intravenous injections on three consecutive days and resting four days. The animals were bled and the serums of 18 and 19 gave a precipitin titer of 1 to 1280 and that of 20 of 1 to 640. Rabbit 18, immune to

filtrate when exposed to a rabbit infected with Hemophilus influenzæ, did not become infected.

An effort was made to immunize a rabbit to heated culture filtrate. Culture filtrate heated to 100° C. for one hour was used.

RABBIT 21. Received repeated injections of heated filtrate, given in the same manner as described for Rabbits 18 to 20, was exposed to an infected rabbit with open lesions. At the time of exposure, the serum of this rabbit gave a precipitin titer of 1 to 40, the precipitin titer of this same rabbit before the series of injections being negative. Rabbit 21 became ill within three days and died in eight days. At autopsy, the small bronchi were congested, the lungs were hemorrhagic and there was a serous exudate in the pleural cavity. The heart was enlarged. Hemophilus influenzæ was recovered from the heart blood, lungs and pleural exudate.

The above experiments show that rabbits can be immunized to unheated culture filtrate, and following immunization can be exposed to infected rabbits, without becoming infected. On the other hand, a rabbit receiving repeated injections of heated culture filtrate, when exposed to an infected rabbit develops the infection. It thus appears that heating a culture filtrate to 100° C. for one hour destroys its property of exciting protective antibodies in rabbits.

8. *Experiments with Culture Filtrates in Collodion Sacs.* A sealed collodion sac containing culture filtrate of the Hammett strain was placed into the peritoneal cavity of a rabbit. The experiment was performed in the following manner:

RABBIT 22. A collodion sac containing 3 cc. of brown blood-broth culture filtrate, freshly prepared, to which had been added 3 cc. of sterile brown blood broth was placed into the peritoneal cavity of the rabbit. Three months later, the serum of the rabbit showed a precipitin titer of 1 to 1280. Eight months later, the precipitin titer had fallen to 1 to 640. While the experiment was performed on only one rabbit, the opinion might be advanced that the toxic agent of the culture filtrate continued to remain active, in the collodion sac, and that the animal developed some immunity against it.

RABBIT 23. A collodion sac containing 4 cc. of brown blood broth Hemophilus influenzæ culture (Hammett strain) was placed into the peritoneal cavity of a rabbit. The next day, the animal was dead. On autopsy, it was found that the rabbit died of acute peritonitis, and that the collodion sac had broken. Pure cultures of Hemophilus influenzæ were recovered from the peritoneal pus, and the heart blood.

Conclusions on Rabbit Experiments. 1. For Hemophilus influenzæ (Hammett strain) 1 billion living organisms injected intravenously kill rabbits in eighteen hours, and produce lesions similar to those found in humans dying of influenza.

2. Living organisms of virulent strains of Hemophilus influenzæ are not as quickly fatal when injected subcutaneously as cultures injected intravenously, since chronic abscesses are formed in the former procedure from which pure cultures of Hemophilus influenzæ may be recovered several months after the initial injection.

3. Attempts at immunization of rabbits with a virulent strain of Hemophilus influenzæ failed, due to the pathogenicity of the organism. With the methods employed, the animals lost weight and local abscesses were formed when an attempt was made to administer living organisms. The agglutinin titer of the serum was only 1 to 320.

4. Normal rabbits may become infected when brought in contact with rabbits previously infected with Hemophilus influenzæ and having open lesions.

5. Rabbits previously injected with a sublethal dose of culture filtrate, will, when immediately exposed to an infected rabbit, acquire the infection and succumb sooner to this infection than would a normal rabbit if exposed to an infected rabbit. The culture filtrate appears to contain a toxic agent, which promotes infection with Hemophilus influenzæ, since infection took place sooner when a sublethal dose of filtrate was administered before exposure. The theory may be advanced that a toxic agent is present in culture filtrates of virulent strains of Hemophilus influenzæ and that it may act as an aggressin to infection with the organism.

6. Culture filtrates of a virulent strain of Hemophilus influenzæ, when injected intravenously into rabbits, can cause death. Parker[2] and Wollstein[3] also found that Hemophilus influenzæ produced a filtrable poison which was lethal for rabbits when injected intravenously.

7. Rabbits may be immunized to culture filtrates and when exposed later to infected rabbits, be immune to infection. Parker[2] also immunized rabbits to at least four or five times the M.L.D.

8. Culture filtrates heated to 100° C. for one hour previous to injection failed to immunize rabbits to the point of protection when exposed to infected rabbits. Parker[2] also found that filtrate poison when heated to 55° C. for one-half hour was partly destroyed, and when heated to 75° C. for one hour, or boiled for five minutes, over two-thirds the toxicity had been lost.

9. When a collodion sac containing culture filtrate was placed in the peritoneum of a rabbit, the serum developed a precipitin titer as high as 1 to 1280.

(*d*) **Biologic Studies on Hemophilus Influenzæ.** The biologic characteristics of all strains used in this study were determined, that is, the Hammett strain, the animal passage cultures of the Hammett strain and the strains isolated from other patients.

1. All strains plated to ascertain if the peculiar mouse-like odor was present gave positive results.

2. Hemolysis: Not any of the strains studied showed hemolysis in blood-broth cultures.

3. Litmus milk reactions: None of the strains studied gave any change in litmus milk after seven days at 37.5° C.

4. Association with Staphylococcus aureus: All strains studied

showed definite increase in the size of the colonies when grown in association with Staphylococcus aureus on red blood agar plates.

5. Indol formation: The Hammett strain and the animal passage strain originating therefrom all produced indol.

Of twenty-two other strains isolated from patients, fourteen produced indol, and eight were negative. Of the fourteen strains producing indol, only seven were virulent. The virulence of a strain and its ability to form indol are apparently not closely related.

6. Growth on plain infusion agar without blood: All strains were plated on plain beef infusion agar, pH 7.6, and none gave growth.

The above tests show that typical cultures of Hemophilus influenzæ were used for the experiment, and, as has also been shown by Rivers[4,5] that no biologic classification could be made of them. Table II shows the biologic characteristics of twenty-three strains of Hemophilus influenzæ. The fifteen animal passage generations of the original Hammett strain gave the same cultural characteristics of the parent strain.

(*e*) **Serologic Reactions.** Each of the strains of Hemophilus influenzæ included in this study was tested by agglutinative and precipitin reactions with immune serum (horse) of the Hammett strain. The technique employed in these tests was as follows:

1. *Agglutinative Reactions.* The agglutination technique followed was according to the method of Small and Evans.[6] The cultures of Hemophilus influenzæ were streaked on brown blood agar plates and these plates were incubated over night at 37.5° C. The resulting growth was washed off in infusion broth. The suspensions were first centrifugalized to throw down agar particles and then centrifugalized at high speed for forty-five minutes to sediment the bacteria. The supernatant fluid was decanted, and the sediment of microörganisms resuspended in infusion broth, and heated at 85° C. for one hour. The suspension was then standardized to 1 billion microörganisms per cubic centimeter and agglutination tests performed with immune serum diluted 1 to 200. This made the final dilution 1 to 400. The tests were incubated in a water bath at 50° C. for eighteen hours. Naked eye readings were made.

2. *Precipitin Reactions.* The precipitin technique used was according to the following method: Eighteen-hour brown blood-broth cultures were filtered through a grade N. Berkefeld filter and the filtrate was tested for sterility. Immune serum (horse) of the Hammett strain was diluted from 1 to 10 up to 1 to 2560. Equal amounts of culture filtrate was added to the diluted serum and the tests remained at room temperature for eighteen hours. Naked eye readings were made of the precipitation next morning.

Table II shows the precipitin and agglutinative reactions of the twenty-three strains of Hemophilus influenzæ studied.

The homologous strain and each of its animal passage subcultures were all agglutinated by the immune horse serum of the

Hammett strain. Of the twenty-two strains from other patients eighteen were agglutinated and four were not agglutinated. Thus, there was a high percentage of immunologic relation of these strains studied.

TABLE II.—CULTURAL CHARACTERISTICS, PRECIPITIN, AGGLUTINATIVE REACTIONS AND VIRULENCE OF TWENTY-THREE STRAINS OF HEMOPHILUS INFLUENZÆ.

Strain.	Source.	Associated with Staphylococcus aureus.	Odor.	Growth on plain infusion agar.	Indol.	Litmus milk.	Hemolysis.	Agglutination with immune serum of the Hammett strain.	Precipitin formation with immune serum of Hammett strain.	Virulence.
Hammett	Sputum	+	+	−	+	−	−	+	+	+
F 1 . .	Sputum	+	+	−	−	−	−	+	+	+
F 2 . .	Sputum	+	+	−	+	−	−	+	−	−
F 3 . .	Sputum	+	+	−	−	−	−	+	+	+
F 4 . .	Sputum	+	+	−	−	−	−	+	+	+
F 5 . .	Sputum	+	+	−	+	−	−	−	−	−
F 6 . .	Sputum	+	+	−	−	−	−	−	−	+
F 7 . .	Sputum	+	+	−	+	−	−	+	−	−
F 8 . .	Sputum	+	+	−	+	−	−	+	−	−
F 9 . .	Sputum	+	+	−	+	−	−	+	−	−
F10 . .	Sputum	+	+	−	−	−	−	+	+	+
F11 . .	Sputum	+	+	−	+	−	−	+	−	−
F12 . .	Bronchoscopic sputum	+	+	−	+	−	−	−	−	+
F13 . .	Bronchoscopic sputum	+	+	−	−	−	−	−	−	−
F14 . .	Bronchoscopic sputum	+	+	−	−	−	−	+	−	−
F15 . .	Bronchoscopic sputum	+	+	−	+	−	−	+	−	−
F16 . .	Spinal fluid	+	+	−	+	−	−	+	+	+
F17 . .	Spinal fluid	+	+	−	+	−	−	+	+	+
F18 . .	Spinal fluid	+	+	−	+	−	−	+	+	+
F19 . .	Spinal fluid	+	+	−	+	−	−	+	+	+
F20 . .	Pleural fluid	+	+	−	−	−	−	+	−	−
F21 . .	Pleural fluid	+	+	−	+	−	−	+	+	+
F22 . .	Nasal culture	+	+	−	+	−	−	+	+	+
		23+	23+	23−	15+	23−	23−	19+	11+	13+

The homologous strain and each of the cultures recovered from animal passage of this strain, gave positive precipitin reactions with its immune serum up to a dilution of 1 to 640.

Of the twenty-two other strains ten gave precipitin reactions with this serum and twelve gave negative results. In order to correlate the serologic reactions with the virulence of the several

strains, the results of the virulence test are set down in Table II for each strain.

It will be noted that eighteen of the twenty-two other strains showed agglutination. Of these eighteen strains ten gave precipitin reactions and all of these ten were virulent. Each of these ten strain gave positive precipitin reactions with the immune horse serum (Hammett strain) in dilutions of 1 to 160. None were higher.

Thus it would appear that the precipitinogens are present and are related to the toxic agent in the culture filtrate of virulent strains that agglutinate with the immune horse serum.

(*f*) **Therapeutic Application of Hemophilus Influenzæ Immune Serum.**

1. *Serum Preparation and Titration.* Because of extreme toxicity of the Hammett strain, this culture was selected to immunize a horse, in an effort to prepare an immune serum in quantities sufficient for adequate therapeutic tests in patients presenting clinical influenza.

In immunization of the horse difficulties were encountered due to the high pathogenicity of the organism. At first small amounts of killed microörganisms suspended in physiologic salt solution were injected subcutaneously. Later, living microörganisms were given subcutaneously. The injection of viable cultures subcutaneously produced abscesses and it was discontinued in favor of killed microorganisms suspended in unheated culture filtrate. Again with this combination, large abscesses were formed which when cultured were sterile for such bacteria as Staphylococci, Streptococci, or Hemophilus influenzæ. After these attempts treatment was again instituted with killed organisms suspended in physiologic salt solution. After eighteen months the serum gave an agglutinin titer of 1 to 2560 and a precipitin titer of 1 to 640.

The protective value of the immune serum has been tested on mice as follows. Killing doses, $\frac{1}{8}$ billion organisms per cc. of the Hammett strain were given intraperitoneally, followed in thirty minutes by 2 cc. of immune serum. Experiments have shown that 2 cc. of immune serum has the value of protecting mice against five killing doses of the microörganism. Controls were run on these experiments to be sure that the quantity of organisms would actually kill.

The serum has also been tested in the same way with other strains that agglutinated with the immune serum and here high protection was also manifested.

Because of the demonstrable antibodies in this serum which are capable of protecting mice against lethal doses of Hemophilus influenzæ, (that is, the Hammett strain, and other virulent strains which show positive precipitin against the immune serum) it was decided to apply it clinically in typical acute influenza to test whether it had any effect on the toxemia of this disease.

The serum has been collected from five bleedings of the horse,

approximately eight liters each and has been preserved in ampules and stored for further favorable opportunity for use. The horse is continued under treatment in an effort to maintain a high-grade of immunity.

2. *Therapeutic Use of the Serum.* Opportunity for such testing was limited to 3 cases of typical acute influenza of the respiratory type, and 4 of meningitis due to Hemophilus influenzæ.

Case Reports. *Influenza, Respiratory Type.* Only 3 cases with typical acute influenza within the first forty-eight hours of the disease were available for serum treatment.

CASE I.—(Patient of Dr. Diehl.) Male, colored, aged forty-two years, complained of soreness throughout body, cough and expectoration, and extreme pain in the eyeballs. The attack occurred in the morning, accompanied by chills. In the afternoon, when brought to the hospital, he had a temperature of 102.5° F. and was acutely ill. Sputum cultures showed Hemophilus influenzæ predominating, accompanied by Streptococcus mitior. The white blood cell count was 4300. A clinical diagnosis of influenza was made. Twenty cubic centimeters of influenzæ immune serum were given intramuscularly at 5 P.M. Next morning by 11 A.M. the temperature had dropped to 98.5° F., and the white blood cell count was 9800. For twenty-four hours, the temperature continued normal and the white blood cell count was 7500. The patient felt well and continued to feel so until discharged from the hospital ten days later. The noticeable point in the convalescence of the patient was the feeling of well being in contrast to the usual symptoms of weakness and depression following an attack of influenza.

CASE II.—(Patient of Dr. Lanyon.) Male, white, aged thirty years, employee in the hospital, complaining of soreness throughout the body, accompanied by chills and having a temperature of 103° F. A white blood cell count showed a leukopenia of 4000. Nasal cultures showed pure culture of Hemophilus influenzæ and throat cultures showed Hemophilus influenzæ predominating, accompanied by pneumococcus, Group 4 and Streptococcus mitior. Twenty cubic centimeters of influenza immune serum were given intramuscularly on the first day of illness. Next morning the temperature was normal, and the white blood cell count was 8500. The patient felt very well and continued to do so until his return to work. He also had none of the symptoms following influenza, such as weakness and depression.

CASE III.—(Patient of Dr. Lanyon.) A young adult male with a clinical diagnosis of influenza, accompanied by high temperature and a leukopenia. Twenty cubic centimeters of influenza serum were given on the first day of illness intramuscularly followed by recovery of the patient within twenty-four hours.

Meningitis Due to Hemophilus Influenzæ. Four patients with meningitis were also treated. They were young children showing pure culture of Hemophilus influenzæ in the spinal fluid. The immune serum was given intravenously and intraspinally, and although brief, temporary improvement was reported by the clinicians, all cases proved fatal. A fourth patient, an eighteen-month-old boy, showing pure culture of Hemophilus influenzæ in the spinal fluid, was

treated with the serum. A trephine operation was performed and the spinal canal washed with serum. The serum was also administered intravenously. This patient lived for twelve days following the beginning of serum treatment. On the twelfth day the patient died.

The application of the antiserum in these few cases is presented simply as a matter of record and for the sake of completeness in reporting the work undertaken. No inference as to any possible therapeutic value is implied. Our purpose has been that of preparing a potent antiserum against a very virulent strain of Hemophilus influenzæ and storing it in sufficient quantity to test it out in clinical influenza should this disease return in epidemic prevalence. Only in this manner can it be determined whether the clinical toxemia of epidemic influenza is in any way related to the toxic agents in cultures of Hemophilus influenzæ.

Conclusions. 1. Virulence of strains of Hemophilus influenzæ may be maintained by keeping the cultures in suitable fluid media at a room temperature of 18° to 20° C. Of the twenty-three strains studied thirteen were virulent, and ten were avirulent to laboratory animals.

2. Rabbits and mice succumb to inoculation with virulent strains of Hemophilus influenzæ. They also succumb to injections of culture filtrates of virulent strains. Thus the toxic agent causing the virulence of the strain is found in the culture filtrate.

3. Normal rabbits exposed to infected rabbits become infected by contact and death ensues in ten days with characteristic lesions found at autopsy. It also appears that previous treatment of a rabbit with a sublethal dose of culture filtrate hastens the contact infection of that rabbit with Hemophilus influenzæ when it is exposed to an infected rabbit.

4. Skin reactions may be performed on human beings with culture filtrate of a virulent strain, giving positive results with a dilution of 1 to 7000. This test seems to be of the nature of the Dick or Schick reactions, and might perhaps be used to determine susceptibility to infection of humans with Hemophilus influenzæ.

5. Precipitin and agglutinin reactions have been performed on the twenty-three strains studied, using the antiserum prepared with the Hammett strain. Nineteen agglutinated, eleven of which gave a precipitin reaction with the immune serum. Only the strains that gave both positive agglutinin reactions with the immune serum and were also virulent gave precipitin reactions. Precipitin reactions apparently shows a strict parallelism to the virulence in strains of Hemophilus influenzæ.

6. The serum of a horse immunized with a virulent strain (Hammett) was found to protect mice against four to five lethal doses of Hemophilus influenzæ. A few trials of the serum in patients are recorded.

7. It would appear that infection with Hemophilus influenzæ is in direct relation with the pathogenicity of the strain, and that the pathogenicity is dependent upon the association of the organism with a toxic agent which may readily be identified in culture filtrate.

NOTE.—The author wishes to express her appreciation of the advice, assistance and encouragement received from Dr. A. C. Abbott, Dr. D. H. Bergey, Dr. H. F. Smyth and Dr. M. S. Iszard of the School of Public Health and Hygiene, University of Pennsylvania, and also to Dr. J. C. Small, Dr. William Kriedler, Dr. William Belk and Dr. H. D. Palmer of the Philadelphia General Hospital.

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POOLED ADULT BLOOD SERUM AS A PROPHYLACTIC MEASURE IN A MEASLES EPIDEMIC IN AN INSTITUTION.*

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MEASLES is so common a disease and frequently so mild an infection that the laity, and even doctors and nurses, fail to show the proper respect for its dangers. In fact, the mild manifestations so frequently shown lead to a reprehensible laxity in the prevention of the spread of the disease. While it is true that the disease may be mild in its constitutional reactions, it is often a severe affection, threatening life as well as causing unfortunate complications and sequelæ. In children under one year, measles itself produces a very high mortality. In older children, up to four years of age, complicating pneumonias often cause death. Later, while the mortality rate is lower, other complications and sequelæ arise. Even if the disease should run a mild and uncomplicated course, it may lower the resistance to such a degree as to activate a more dangerous process, since there is a close relationship between measles and

* Read before the Philadelphia Pediatric Society, March 12, 1929.

tuberculosis. In children with a latent tuberculosis, measles often provides the spark for the flare-up. Miliary or pulmonary tuberculosis may follow an attack of measles. Tuberculous adenitis and tuberculosis of the bones and joints may appear as a late development. Realizing, then, the serious consequences of this disease, it is obvious that the wilful exposure of children to the infection is fraught with tragic possibilities. Prevention of the disease, surely, is desirable. The first step toward this end is overcoming the ignorance of the public with educational propaganda. The second step is the development of a systematic method of prevention by medical science. What problems does this prophylaxis present?

One great problem in prevention of measles arises from the fact that many contacts occur during the preëruptive catarrhal stage when the diagnosis is yet in doubt. During those months of the greatest prevalence of measles there are always so many cases of cold, grippe and other catarrhal respiratory conditions, that it is impossible to make an accurate or dependable differential diagnosis until the more definite signs of measles become apparent. By that time, one case will have made contacts with many other children in school and elsewhere, and many of these developing the disease, will in like manner, transmit it to others; so that before much time has elapsed a large epidemic has developed. Even with the isolation of all cases diagnosed, spreading will not be checked because of these contacts made during the catarrhal stage. In large epidemics, the closure of the schools, places of amusement and churches would materially lessen the incidence, but apart from its impracticability, what of the children of preschool age and those massed in institutions, involuntary contacts before isolation can be carried out? For their safety, some method of definite immunizing value should be sought, in fact is being investigated now. The developments during recent years indicate that definite progress is being made. As the result of immunization, known contacts have escaped the disease entirely or have been partially protected as evidenced by extremely mild infections.

The etiology of measles has been studied by a host of observers, many of whom have reported the most diverse agents or factors as the possible causes of this disease. None of these factors has ever been proved the cause of measles. In more recent years, another group of factors has been brought forward, including a filtrable virus, a green-producing diplococcus, another diplococcus surrounded by a slight clear halo and a definite streptococcus. The green-producing diplococcus was first discovered by Tunnicliff[1] in 1917. This diplococcus she isolated from blood of patients ill with measles during the preëruptive and eruptive stages. She and her coworkers since that time have published the results of extensive researches made along this line.

In 1923, Coronia[2] and his associates in Italy, reported the isolation of an anaërobic diplococcus. They also have made extensive researches with their organism obtaining results comparable to those of the Tunnicliff laboratory. Ferry and Fischer,[3] in 1926, isolated a streptococcus which they claim as the cause of the disease. Degkwitz[4] goes into the realm of ultramicroscopy, supporting a theory instead of a discovery, and believes that a filtrable virus is the cause. Other investigators support the filtrable virus theory, including Park,[5] who feels that such a theory is more tenable on account of the long incubation period of measles. Therefore, at the present time, there are three schools of thought as regards the etiology of measles. It seems quite likely that two, at least, are working with the same factor, the difference in their results being due to the variations in procedure and interpretation of findings.

Measles, however, has been produced experimentally, both in man and animals, by the inoculation of infective material: blood, nasopharyngeal and tissue cultures which contain the infecting organism, whatever it is proved to be. Whether or not the inoculated type of measles is a truly typical disease as in almost all cases of so-called successful inoculation, the disease is seen in a modified or attenuated form, certainly it does confer an immunity against measles. Natural immunity is often seen in very young children, but persists for life in only a few. The immunity commonly seen in infants may be transmitted through the breast milk, but it seems more likely that natural immunity is transmitted from the mother to the fetus through the placental circulation during gestation. That even this is not infallible has been proved by reports in the literature of mothers, who although they had had the disease during pregnancy did not confer immunity upon their children, since they later developed measles. The duration of the natural immunity is variable and may not last beyond the first year of life. This fact gives rise to the large degree of susceptibility among children.

The aim of prophylactic measures has been to develop a method to decrease the susceptibles, which is possible by certain forms of immunization. Because of the short duration of passive immunity, active immunization has been attempted. This is called morbillization and the term "sero-attenuation" has also come to be used. Herrman,[6] in 1914, reported his success in inducing a mild form of the disease in young infants by inoculating these infants by means of gently rubbing the nasal mucosa with nasal washings collected from measles patients just prior to the appearance of the eruption. He felt that the immunity developing as a result of the mild atypical disease thus produced lasted for some time, at least two years. Hiraishi and Okamato[7] attempted active immunization by small repeated doses of infected blood. Degkwitz[8] injected cultures of conjunctival and pharyngeal secretions in order to produce active immunization. Nicolle and Conseil[9] used a serovaccination method

using first convalescent blood serum followed by blood from patients with active measles. Other investigators have attempted active immunization by somewhat similar methods. Despite all these efforts, the present status of active immunization is still in the experimental stage and while it is hoped that the longer protective methods will soon be available, for the present the fairly assured protection of passive immunization should be tried.

There are several methods of passive immunization, the most widely used being measles convalescent serum. Weisbecker,[10] in 1896, in Germany published the first report of measles convalescent serum which he used for active therapy of the disease. Cenci[11] seems to have been the first to use convalescent serum for passive immunization. A very great many observers have published their results with this method. This convalescent serum is procured from patients within ten days after defervescence of the disease.

On account of the necessarily limited supply of human convalescent serum, an endeavor is now being made chiefly by Tunnicliff and her associates to produce concentrated animal serum for general use. Of the various animals so far tested, goat serum seems to offer the least amount of reaction although horse serum also is used in the preparation of the antiserum as for other infectious diseases. So far, the sera either have not been satisfactory, or have been so limited in quantity, that they are not available for general use. As regards the convalescent serum in Philadelphia, a certain supply is available at the Philadelphia Hospital for Contagious Diseases, but only in a quantity to supply their own expected needs.

Silverman[12] recently reported very interesting results obtained by himself and others using convalescent serum in community epidemic. Through the local bureau of health, blood was collected from convalescent measles patients, by health officers or by the family physicians. By using the serum thus collected definite protection was afforded the susceptibles who seemed likely to develop the disease. By this means, as well as by the mechanical isolation, the particular epidemic was controlled. It is interesting to note, in passing, that the serum of Ferry and Fischer did not give Silverman satisfactory results.

It is a well-established fact, that one attack of measles usually confers a life-long immunity. It is reasonable to conclude, therefore, that the antibodies developed in the blood during an attack of the disease, will persist in adult life. If this be true, then the use of a serum of an adult who has had the disease, might be effective as a preventive measure. When, therefore, it became necessary to cope with an epidemic of measles which broke out among the children of the Southern Home for Destitute Children, the thought of using the pooled sera of the parents occurred to us.

During March and April, 1928, an epidemic of measles occurred in this Home. This outbreak was coincident with an epidemic of

the disease among school children of the Philadelphia area. The source of the outbreak in the home was quite apparent, as all of the children of school age attend the public schools. The extent of the epidemic in the city and the number of cases developing made it necessary to attempt to limit the spread of the infection. As it was impossible to procure sufficient convalescent measles serum, from our patients or elsewhere, to insure a dosage sufficient to protect the susceptibles, and as no measles streptococcus antitoxin or animal serum was available for immediate use, it was decided to use adult serum, the donors being parents of children in the Home.

In the epidemic with which we dealt, owing to the contact of our children with public school children, as well as with each other, ten children developed typical measles, between March 24 and April 11. Our total population at that time was 100 children. Forty-five children had had measles in the Home or gave histories of having had measles prior to admission. There remained in the institution 55 children who gave no history of having had measles, a large majority of whom were, therefore, susceptible. Our problem was to give protection to these children, if it were possible. To obtain an adequate supply of serum, volunteers from the parents of the children were called upon. Each donor was questioned for a history of measles and only those who gave a positive history were used. From each donor enough blood was put into a sterile test tube for a Wassermann test and the tube was properly labelled. Then as much blood as could be conveniently removed was run into an Erlenmayer flask, which was provided with a two-holed rubber stopper into which glass tubing was inserted. One set of tubing was bent at an angle and used for aspiration to increase the flow. To the other a needle with necessary rubber attachment was fastened. All apparatus was sterilized before use, and the blood was withdrawn under aseptic precautions. The blood was set aside in the refrigerator to clot and the serum later decanted, or when necessary, centrifugalized. All the Wassermann-negative and sterile sera were pooled and divided and poured into small vials.

Owing to the length of time necessary for collecting the blood, it was done on two different days, and each day's collection went into separate pools. The inoculations were made as soon as the sera was ready. The first collection immunized 35 children and the second collection immunized the remaining 20 susceptibles.

On April 15 and April 22, the 55 susceptibles were inoculated with 5 cc. of the pooled sera by injection into the buttocks. The children were graded according to contact with the children sick with measles and according to age; and those in closest contact, and next, the young children were inoculated in order named. No untoward reactions followed nor did any fresh cases of measles follow nor did any fresh cases of measles develop.

The following questions arise: had we reached the end of a self-

limited epidemic, or had the epidemic been limited by isolation and hygienic management, or was the absence of new cases due to the definite protection of the serum? In answer to the first, we must remember that the epidemic in the city was still going on, and that our apparently well children were going daily to the public schools. As to the second, although the cases of measles were isolated as soon as a definite diagnosis was possible, there still existed contacts within the Home of susceptibles with the early measles cases having catarrhal symptoms. It, therefore, seems reasonable to conclude that the prophylaxis by the injection of adult serum was effective.

On April 23, however, one child showed a rash not typically morbilliform in character, and had a slight rise in temperature, without however, developing any prodromal coryzal symptoms, or Koplik spots. This reaction first thought to be a serum (anaphylactic) reaction, proved to be German measles. Seventeen other cases followed between April 23 and May 1, 8 of whom had not been given the serum because of a proven positive history of a previous attack of true measles. These cases ran the brief course usual in German measles and showed all its characteristic symptoms; nor was there any difference in the course between the 10 who had received the adult serum and the 8 who did not. Two of the original 10 cases of genuine measles were included in the 18 who later had German measles.

Shaw[13] states that in German measles the susceptibility varies in different epidemics, though it is usually low: about 30 per cent of the individuals exposed. He also states that one attack usually confers immunity for life, although second attacks have been reported. Since, therefore, the pooled sera which we used, probably contained relatively few antibodies against German measles, by reason of the dilution and original small amount present we were not disappointed at its failure to provide protection against German measles as well as it did against true measles.

The use of the serum of adults with a history positive for measles we considered as an original procedure but in looking up the literature it was found that Degkwitz[14] had recommended it, and that von Torday[15] had reported 116 injections with failure to obtain protection in only 12 cases. Reitschel,[16] Jervill[17] Hilsinger,[18] Goebel,[19] Kovacs[20] and Bivings,[21] have all used such serum but in quantities of 20 to 30 cc., which was much greater than the amount which we used. Some reported successful protection, while in others a modified measles developed. In the Southern Home, the 55 susceptibles who received the serum intramuscularly have up to this time apparently been protected, although 10 of these children have had an attack of German measles.

It has been suggested by Hilsinger that the effect of inoculation might be due to nonspecific agents in the serum. This thought has

also occurred to us, although in our series of cases, not one case of measles followed the injection of the adult serum, although 10 cases of German measles did. Are we to assume then that the infective agents of measles are more susceptible to the nonspecific agencies contained in adult blood than the infective agents of German measles? It seems more likely to have been the result of an insufficient concentration of German-measles antibodies.

Summary. 1. Fifty-five susceptible children all of whom had been exposed to measles were inoculated with pooled (Wassermann-negative) adult serum. Those in closest contact and then the younger children were inoculated with the first blood collected, as probably greater risks.

None of the children receiving the serum developed measles; nor had attenuated or modified measles.

2. Eighteen children of the Institution later had attacks of German measles. Of these 10 had received the serum, and 8 had not. (The latter had a positive history of a previous attack of true measles.) Two of the children attacked by German measles, were among the original 10 who contracted measles between March 23 and April 11.

Conclusions. 1. Measles is frequently too carelessly considered by the laity and even by the medical man. It constitutes a grave illness in all children affected under one year of age; while in its complications, it threatens the health and even life of older children. In delicate and pretuberculous children, it often is an activator for the various forms of tuberculosis.

2. Despite the almost universal susceptibility of the disease, prophylaxis against it is worth the effort, since, if it succeeds only in delaying the time of the onset, many lives will be saved.

3. Although the etiology of measles is the subject of investigations of many talented workers, the specific infecting agent has not been convincingly demonstrated. Various sera have been experimentally collected, but have given indifferent results in clinical tests. The blood (whole and serum) of convalescent patients, however, contains specific antibodies, since its injection has given uniformly good results, either entirely preventing the disease or producing an aborted or attenuated form, which has nevertheless, produced a lasting immunity.

4. Since the amounts of convalescent serum are manifestly very limited, and since the disease spreads so rapidly and is difficult to control by reason of many unsuspected contacts, some more practical means of prevention should be tried. Considering that one attack of measles usually gives immunity for life, the serum of adults having had the disease presumably contains the antibodies. On this presumption, the injection of adult serum should help to prevent the spread of measles, particularly in an institution for children, who are at once confined and yet exposed to contacts.

5. In an epidemic in 1928 among the school children of Philadelphia, adult pooled serum, collected from the serum, collected from the parents of children in the Southern Home, was injected in 5-cc. doses to susceptibles in the Home, without the development of one case of measles even of an attenuated form. Apart from all the possibilities of chance which might have produced this result, the effect was so satisfactory that the use of pooled adult serum in similar outbreaks should be encouraged.

NOTE.—We wish to acknowledge our indebtedness to Miss Frieda Ward for collecting and preparing the serum.

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EOSINOPHILIA IN LIVER DIET.

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Introductory Remarks. In their paper of 1927, "A Diet Rich in Liver in the Treatment of Pernicious Anemia," Minot and Murphy[1] mention that they have frequently observed a marked eosinophilia in patients on liver treatment, and they say: ". . . within a few weeks after the diet was begun, the polymorphonuclear eosinophils occasionally increased to beyond 20 per cent, this increase persisting for many weeks."

This observation has been confirmed by many other clinicians, and short remarks on this finding are often met with in the mass of papers already published on the liver therapy.

But only a few authors who have studied the blood picture of the white corpuscles in connection with liver diet, are paying any particular attention to the eosinophilia. Watkins and Berglund[2] state that in their case the number of eosinophils began to increase after three weeks of treatment, and they take the eosinophilia as being due to overdosage of liver. In 4 patients, Whitby[3] found eosinophilia to set in at a similar point of time in the treatment, and in mentioning this finding he gives some hypotheses as to its nature: "The eosinophilia seems to be a part of the patient's reaction to the treatment, and the transient nature of the phenomenon points to a parallel between the reticulocyte reaction and the increase in eosinophils;" later he says: "It is conceivable, therefore, that eosinophilia will be found to be another favorable prognostic sign;" and later: "If anything, the phenomenon is another point in favor of attributing the beneficial effect of liver to its action on the bone-marrow."

In a subsequent paper, however, Smith and Whitby[4] report that they also found eosinophilia—amounting even to 61 per cent—in a series of young people convalescing after various diseases in whom liver therapy had been instituted. Consequent to the above-cited views they also take the eosinophilia in these convalescents to indicate a stimulating effect of the liver treatment on the bone marrow.

Later publications on the liver therapy, in which the treatment with liver extract becomes more predominant, do not mention any presence of eosinophilia. Ordway and Gorham,[5] to be sure, do mention the occurrence of eosinophilia in their material, but it does not appear from their report whether this was observed in patients on liver diet or in patients treated with extract. Whenever the reports on extract-treated patients give details of the white blood findings, there is no evidence of eosinophilia.

Still, the occurrence of eosinophilia in pernicious anemia on liver diet is a peculiar phenomenon. For in pernicious anemia the general rule is that the polymorphonuclear eosinophils are reduced in number or lacking altogether.

Author's Investigations. As we thought that we had become aware of certain principal lines in this problem, we have tried to throw some further light on this question by going through our material of liver-treated patients with pernicious anemia. In 37 of our 54 cases we have differential counts which are serviceable for a survey, although they might have been made more frequently and more regularly. With a view to the present question, we have further treated a number of control individuals suffering from various diseases with liver in one form or other, and we have watched the white blood picture in these persons.

The differential counts are made on cover-slip preparations, and 100 cells are counted in each specimen. Six per cent eosinophils is taken as the upper limit of the designation: no eosinophilia.

As the development of eosinophilia in our experiments has proved to depend on the form in which the liver is ingested, our results will be mentioned in sequence as the results of treatment with: (*a*) Raw liver; (*b*) fried liver; (*c*) liver extract; (*d*) results of alternating or mixed treatment.

(*a*) *Treatment with Raw Liver.* Calf liver is used throughout. The liver was ground very finely and given in wafers or as a beverage together with orange juice. At first, in 1927, the doses were small, but the initial dose was soon increased to 200 or 300 gm. a day, and a similar or somewhat smaller amount was given as maintenance dose. All told, 22 patients were treated for longer periods with raw liver alone. A few of these have kept on taking raw liver, others have gradually turned to mixed treatment or to treatment with extract alone; finally, a few patients who were previously treated with extract, have, for the sake of experiment, been treated periodically with raw liver.

During the treatment there developed a marked degree of eosinophilia in the great majority of these patients. When the liver is given in large daily doses, the eosinophilia usually appears in about four weeks, although it may take a longer time in some cases. As a rule, the eosinophilia sets in rather suddenly and attains some quite high values: 20, 40, nay, even as high as 74 per cent has been observed in one of our cases (Table I). Once the eosinophilia has appeared, it may vary some in value from one examination to another, but otherwise it seems to keep up as long as the administration of raw liver is kept up—at any rate, we have seen it to persist in patients who were getting this treatment for about two years.

TABLE I (F.M.H.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Mast.	Treatment.
Aug. 25, 1927	57	41	1	1	0	Raw liver, increasing to 200 gm.
Jan. 9, 1928	29	18	43	4	5	
Feb. 4	9	13	74	4	0	
Mar. 31	27	27	44	2	0	
April 18	40	19	38	3	0	
June 24	..	..	..	..	..	Liver extract corresponding to 300 gm. of liver.
Aug. 28	57	10	24	10	0	
Dec. 22	56	25	17	2	0	Liver extract corresponding to 100 gm. + fried liver, 125 gm.
Mar. 9, 1929	63	27	6	4	0	Liver extract corresponding to 200 gm.
June 10	50	23	13	4	0	

As is evident from the examples given, the number of eosinophils is increased at the expense of the polymorphonuclear neutrophils, whose number is reduced correspondingly—not only in percentage but also in absolute value; for the slight leukocytosis that is seen in the beginning of the treatment does not continue later on.

As exceptional cases in which the eosinophilia failed to appear, or developed to a slight degree only, we may point out one patient who was treated with raw liver for one and a half years without the eosinophilia ever rising higher than to 10 per cent. He claims he has taken 250 gm. of raw liver a day, but as the rest of the clinical results have been less favorable in his case, we are not fully convinced as to the accuracy of his statement. In another patient, who came under treatment not so long ago, eosinophilia did not appear until after six weeks of treatment, and in the following weeks its values were only 8, 19 and 9 per cent.

Corresponding experiments were carried out on 4 control individuals with a daily dose of 250 gm. of raw calf liver. The clinical diagnoses of these 4 cases were: Chronic endocarditis, acute rheumatic polyarthritis, achylia, gastric ulcer. After about four weeks of treatment all 4 control individuals showed the typical development of a marked eosinophilia. Instances are given in Tables II and III.

TABLE II (K. A. H).—DIAGNOSIS: CHRONIC ENDOCARDITIS.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
Dec. 28, 1928	53	32	6	9	Raw liver, 250 gm.
Jan. 5, 1929	79	14	4	3	
Jan. 11	60	27	8	5	
Jan. 21	55	20	19	9	
Jan. 29	48	15	34	3	
Feb. 5	44	16	37	3	
Feb. 15	31	21	43	5	
Feb. 25	60	18	13	9	

TABLE III (M. J.).—DIAGNOSIS: POLYARTHRITIS RHEUMATICA.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
Sept. 18, 1928	70	21	3	6	Raw liver, 250 gm.
Sept. 27	66	21	5	8	
Oct. 1	69	27	3	1	
Oct. 13	35	19	43	3	
Oct. 23	19	10	67	3	
Nov. 5	30	29	37	4	
Nov. 14	44	20	35	1	
Nov. 23	17	26	54	3	

(*b*) *Treatment with Fried Liver.* Calf liver is used throughout. The liver is fried but slightly so that it is brownish on the outside and reddish in the middle. The dosage has been 250 gm. a day. Only one case of pernicious anemia is treated in this way. The treatment was kept up for three months. There was no eosinophilia; the highest count was 6 per cent (Table IV).

TABLE IV (E.N.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Mar. 13, 1929	62	36	1	1	0	
Mar. 23	44	49	0	8	0	
Mar. 29	..	..	..	..	..	Fried liver, 300 gm.
April 3	80	15	0	5	0	
April 10	71	14	0	12	3	
April 23	58	27	6	8	0	
May 1	69	18	1	13	0	
May 8	67	24	1	8	1	
May 15	55	33	4	8	0	
May 22	60	35	0	10	1	
May 29	51	21	6	18	4	
June 5	54	38	1	7	0	
June 14	67	36	0	7	0	
July 1	61	32	3	4	0	

Three control individuals with the diagnoses: Pleurisy, gastric ulcer, and pleurisy, and 1 normal control individual were treated respectively four, two, two and a half and two months in the same way. Three of the 4 controls showed absolutely no eosinophilia (Table V). In the fourth control individual the count gave 0, 0, 6, 7, 3, 6, 9, 8, 9 and 3 per cent.

TABLE V (S.).—DIAGNOSIS: PLEURITIS.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
April 12, 1929	57	29	5	9	Fried liver, 250 gm.
April 19	63	30	1	6	
April 29	57	31	2	10	
May 5	66	29	1	4	
May 10	62	25	3	10	
May 17	65	32	1	2	
May 24	64	21	1	14	
May 31	60	31	0	9	
June 7	59	25	4	12	
June 15	65	27	2	6	
June 22	66	26	1	7	

(*c*) *Treatment with Liver Extract.* A smaller part of the extract employed is Liver Extract Lilly or some other extract, the chief part

is Extr. Hepatis (Medicinalco, Copenhagen). Usually the initial dose has corresponded to 300 to 600 gm. of liver. As a rule the maintenance dose has corresponded to 200 to 300 gm. of liver, but this dosage has not always been kept up.

Twelve of the patients with pernicious anemia have continuously been treated with extract alone. None of these showed eosinophilia to the same degree as was observed in the patients treated with raw liver, and most of them showed no eosinophilia (Table VI). Two patients showed a slight increase of the eosinophil count (up to 8 and 9 per cent); in 1 patient there was once an apparently accidental increase to 14 per cent; and 1 patient who has been treated and observed for twenty months, showed twice an apparently accidental increase in number of eosinophils amounting to 18 per cent and 27 per cent, respectively. This case, however, may hardly be considered pure, as on a later examination the patient states that he had substituted whole liver for liver extract during a period some time before; but reliable information on this point is not available at the present.

TABLE VI (E. F. L.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Aug. 19, 1928	..	..	..	..	..	Liver extract corresponding to 600 gm.
Aug. 20	31	66	0	2	1	
Sept. 15	63	32	0	5	0	
Sept. 24	59	35	0	6	0	
Oct. 6	50	46	1	3	0	
Oct. 10	..	..	..	..	..	Liver extract corresponding to 300 gm.
Oct. 30	55	35	2	8	0	
Dec. 15	38	50	1	11	0	
Mar. 8, 1929	46	47	0	7	0	

A single control experiment on a patient with phlebitis who got liver extract corresponding to 600 gm. of liver daily for two months, gave no eosinophilia.

(*d*) *Alternating or Mixed Treatment.* More than half of the patients have been subjected to a change in treatment, as a rule in this way, that they were first treated with raw liver and then gradually went on to get liver extract. But, as mentioned, a few patients who had previously been treated with liver extract, were now—for the sake of experiment—put on raw liver.

The results of these changes in treatment have been quite clear-cut when the periods of treatment have been sufficiently long and sufficiently straight. The eosinophilia has gradually subsided on changing from treatment with raw liver to treatment with liver extract. In some of these cases, the eosinophilia disappeared within

a few months (Table VII), in others it persisted for a longer period—up to six months—before it finally went away (Table VIII). Some of these patients may later show an apparently accidental eosinophilia on a single examination, but it is quite reasonable, we think, to regard this as similar to the finding we mentioned in a few of the patients treated with extract alone.

TABLE VII (P. S. R.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Feb. 1, 1928	52	45	3	0	0	Liver extract corresponding to 200 gm.
Feb. 10	45	48	1	6	0	
Feb. 13	..	..	..	..	..	Liver extract corresponding to 300 gm.
Feb. 20	67	21	5	7	0	
Feb. 27	53	35	1	8	3	
Mar. 5	38	57	0	4	1	
Mar. 15	64	22	4	10	0	
April 18	..	..	..	..	..	Liver extract corresponding to 200 gm.
June 19	58	30	3	7	2	
Oct. 1	71	24	2	8	0	Liver extract corresponding to 100 gm.
Dec. 6	48	41	2	9	0	

TABLE VIII (S. E. R.).—DIAGNOSIS: PERNICIOUS ANEMIA. DIABETES MELLITUS.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Nov. 9, 1927	64	32	3	1	0	
Nov. 12	..	..	..	..	..	Raw liver increasing to 200 gm.
Jan. 4, 1928	59	20	14	7	0	
Jan. 14	8	29	51	9	2	
Mar. 17	..	..	..	..	..	Liver extract corresponding to 300 gm.
May 9	60	21	11	8	0	
June 19	52	20	17	5	5	
Aug. 15	62	29	3	6	0	
Oct. 16	68	26	3	3	0	
Oct. 23	68	26	3	3	0	
Nov. 19	61	21	9	7	2	
Dec. 3	60	25	8	7	0	Liver extract corresponding to 200 gm.
Mar. 9, 1929	60	33	3	4	0	

When, on the other hand, the treatment has changed from liver extract to raw liver, eosinophilia has appeared after the usual period, about four weeks, of treatment (Table IX). In such cases, it should be pointed out, the eosinophilia appears at a time when the patient has long ago been compensated for his anemia.

TABLE IX (E.N.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Sept. 8, 1927	..	..	..	..	..	Raw liver, increasing to 200 gm.
Jan. 4, 1928	29	14	49	6	2	
Feb. 15	..	..	..	..	..	Raw liver, 250 gm.
Mar. 9	..	..	..	..	..	Liver extract corresponding to 300 gm.
Mar. 25	57	10	27	6	0	
June 19	43	25	21	9	2	
Aug. 1	67	12	11	10	0	
Aug. 30	..	..	..	..	..	Liver extract corresponding to 100 gm. + 1 liver dish weekly.
Dec. 21	68	23	5	4	0	Liver extract corresponding to 100 gm.
Mar. 7, 1929	59	31	1	9	0	

TABLE X (E.N.) —DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
April 22, 1927	53	40	5	2	0	
May 12	..	..	..	..	..	Raw liver, increasing to 200 gm.
Jan. 6, 1928	47	28	11	12	2	
April 18	35	24	31	10	0	
July 5	..	..	..	..	..	Liver extract corresponding to 200 gm.
Dec. 12	42	42	14	2	0	
Mar. 5, 1929	63	30	2	2	0	
June 5	59	25	20	6	0	

TABLE XI (H.H.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Jan. 12, 1928	56	29	2	7	1	Liver extract corresponding to 300 gm.
Jan. 20	55	37	4	6	8	
Jan. 27	68	26	1	3	2	
Feb. 4	42	40	7	9	1	
Feb. 13	41	45	1	11	2	
Feb. 22	62	26	5	8	0	
Feb. 29	62	18	8	11	1	
Mar. 8	70	20	4	5	1	
April 3	..	..	..	..	..	Raw liver, 300 gm.
May 3	44	15	29	12	0	
May 31	..	..	..	..	..	Liver extract corresponding to 200 gm.
Aug. 3	47	27	17	9	0	
Sept. 4	70	14	13	3	0	
Dec. 18	53	15	26	6	0	
Mar. 4, 1929	66	21	8	4	0	
June 12	63	33	2	2	0	

If the patients have been taking a mixed treatment, partly raw liver, partly fried liver and partly liver extract, either combined or alternating, the eosinophil features will be somewhat "muddled" (Table X).

Discussion. As far as we can see, our investigations demonstrate two points: (1) That eosinophilia, at least in its typical pronounced form, develops only when the treatment is carried out with *raw liver*, and fails to appear on administration of fried liver or liver extract; (2) that this eosinophilia is not characteristic of patients with pernicious anemia, but appears *in other individuals too* on administration of the same quantity of raw liver.

As to the first of these points, it is quite true that treatment with underdone, fried or roasted, liver or with liver extract occasionally is associated with an increase in the number of eosinophils that approaches or exceeds the upper limit of the normal, and that instances of transitory and apparently accidental eosinophilia occasionally occurs in cases treated with liver extract, but this does not alter the main point: that the typical pronounced and persistent form of eosinophilia is encountered only in treatment with raw liver, where it is a very frequent, almost constant, phenomenon.

It is not so easy to say whether we disagree with other investigators on this particular point. For other investigators who mention the eosinophilia, in passing or more in detail, have evidently not paid any attention to this difference in effect of the various methods of administration, and for this reason they do not always state in which form the liver was given. Evidently Whitby has used both raw and prepared ("cooked") liver, and Smith and Whitby mention only "fresh-cooked" liver.

From the control experiments it is obvious that the phenomenon is not characteristic of pernicious anemia, as all the controls turned out positive. This finding suggests by itself that the eosinophilia is no indication of the therapeutic liver effect in pernicious anemia in the same way as, for instance, the reticulocyte reaction. And this conclusion is obvious from the fact that the phenomenon does not appear in treatment with fried liver or liver extract that, therapeutically, has given excellent results, with typical reticulocyte reaction and rise of hemoglobin percentage and erythrocyte count. Even when the doses of liver extract were excessive—corresponding to 600 gm. of liver a day—there was no eosinophilia.

So when Whitby and Smith and Whitby classify the eosinophilia with the reticulocyte reaction as indications of the curative liver effect, we cannot subscribe to this view. On the contrary, *we have to look upon the eosinophilia as a practically accidental by-product in the treatment that has nothing to do with the curative effect.* It seems perfectly unreasonable when Adler and Schiff,[6] after treating 2 normal individuals with "Hepatrat" and finding an increase in eosinophils to 9 and 5 per cent, declare that "diese Tatsachen

sprechen dafür, dass das Hepatrat ein ausgezeichnet wirksamer Leberextrakt ist."

At present we shall not enter into any discussion of what may conceivably be the cause of this eosinophilia but merely mention that, from direct clinical observation, it appears to represent a harmless phenomenon.

Summary. Eosinophilia in liver treatment of pernicious anemia has appeared in a marked and persistent form when the treatment is carried out with raw liver (calf) in large doses. As a rule, the eosinophilia has appeared rather suddenly after about four weeks of treatment, and it has reach to high degrees—20, 40, even 74 per cent. It seems to persist as long as the administration of raw liver is kept up. On treatment with fried liver (calf) or liver extract, the phenomenon has usually been absent; and when present in single instances, it was in a faint and transitory form.

Control individuals suffering from various other diseases have responded to the treatment in the same manner as have patients with pernicious anemia, as they constantly showed eosinophilia on ingestion of raw liver but not after intake of fried liver or liver extract.

This eosinophilia is to be considered a by-product in the treatment of pernicious anemia with raw liver that has nothing to do with the curative effect of the treatment.

As far as directly observable, the eosinophilia represents a harmless phenomenon.

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EOSINOPHILIA WITH SPLENOMEGALY.

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The occurrence of marked eosinophilia together with enlargement of the spleen has been reported a few times in recent years. These cases are of considerable interest, both because of their rarity and because of certain difficulties in classification which they present. At this clinic we have recently observed such a case, both clinically and pathologically.

Case Report. On July 30, 1927, B. N., a man, aged twenty-three years, was admitted to the hospital complaining of pain in the chest, cough and night sweats. His family history was negative apart from the fact that his father was said to be suffering from cancer. The past history included an attack of jaundice at the age of eight years and diphtheria five years previously. He had had frequent attacks of tonsillitis.

A year and a half before admission the patient began to have pain in the left chest, aggravated by motion, coughing and deep breathing. No other symptoms were present until seven months before admission, when, following a tonsillectomy, he began to have a productive cough, fatigue and night sweats. The pain became more sharp and was also felt in the right chest. Four months before admission a diagnosis of pulmonary tuberculosis was made and temporary improvement followed a two weeks' stay in bed. Two weeks before admission he spat up about a cupful of blood.

Physical examination revealed a rather listless young man with pale skin and reddish hair. There were no abnormalities of the head and neck. The chest showed some dullness above the third rib on the left anteriorly, and a patch of râles at the inferior angle of the right scapula. The heart appeared normal. The spleen percussed definitely enlarged, but the edge was not felt. The deep and superficial reflexes were very active and a tremor of the hands was present.

The most interesting laboratory finding was the blood counts, which are charted below.

	July 30, 1927.	August 1, 1927.	Sept. 20, 1927.
Hemoglobin	75%	....	50%
Red blood cells	3,520,000	....	2,780,000
White blood cells	16,000	....	13,450
Polymorphonuclears	26%	48%	33%
Small lymphocytes	13%	14%	8%
Large lymphocytes	0%	2%	3%
Eosinophils	60%	30%	55%
Basophils	1%	0%	1%
Platelets	....	180,000	

The smear showed some variation in size and shape of the red cells. The most striking feature, however, was the fact that the eosinophils were practically all adult forms. Only about 1 per cent of them appeared immature. A large number of them were vacuolated.

The urine showed a small amount of albumin and occasional hyalin casts. Stool examination was negative for ova, parasites and blood. The sputum was twice negative for tubercle bacilli, yeasts and molds. The Giemsa stain showed large numbers of eosinophils. Culture of the sputum yielded a staphylococcus as the predominating organism, with also occasional pneumococci. Microscopic examination of a piece of deltoid muscle was negative for trichinæ. Roentgen rays of the chest showed enlargement of the hylus on both sides, with accentuation of the markings into both upper lobes, and some clouding at the right apex. It was thought to be most suggestive of tuberculosis. A basal metabolism done when the temperature was 100.4° was +35.

The patient was not seen again after the last blood examination on September 20, 1927. His local doctor reported on November 29 that he was weaker and losing weight, with a cough which could only be relieved by morphin. He died, January 4, 1928. An autopsy was done fourteen hours after death at his home, by Dr. George Mackenzie, after the body had been embalmed. His physician reported that prior to death he developed severe pain in his head and nearly lost his sight. Permission to examine the head was not granted.

Autopsy Report (*Abstracted*). The body is that of a young man in fair state of nourishment. The body has already been embalmed and is very rigid throughout. There is an abundant growth of red hair.

There is no free fluid in the abdominal cavity. The lower margin of the liver lies 9 cm. below the xiphoid and 9.5 cm. below the costal border in the midclavicular line. The anterior margin of the spleen does not project below the costal border, but palpation reveals considerable enlargement. The mesenteric lymph nodes are irregularly enlarged, some measuring up to 1.5 cm. in diameter. In the mesentery a calcified node measuring more than 1 cm. in diameter is noted. A small amount of fluid is present in the right pleural cavity. There are dense adhesions at the apices of both lungs.

Heart. The apex of the heart is formed entirely of the left ventricle. In the myocardium of the right ventricle is a small brownish mottled area. There is some thickening of the mitral valve at the free border. A thrombus, 0.5 to 1 cm. in thickness, lines practically the entire cavity of the left ventricle.

Lungs. Section through the apex of the left lung reveals some dark hemorrhagic spots. Numerous similar hemorrhagic blotches are found over the anterior surface of the right upper lobe. Considerable pigmentation is present.

Spleen. The spleen is very large and deeply notched on the anterior margin. It measures 16 by 10 by 6 cm. and weighs 510 gm. The capsule is smooth. In the embalmed state it is dark bluish red.

Microscopic. *Lungs.* Fibrous pleurisy and emphysema are present. The hemorrhagic spots seen in the gross are found to be areas in which the alveoli are packed with red cells and contain pigment-laden wandering cells. In the center of the areas the red cells predominate while at the periphery only a few red cells are seen and the alveoli are crowded with wandering cells, less filled with pigment. In these areas, the alveolar septæ are thickened and crowded with wandering cells and eosinophils and some organization is present.

Heart. A thrombus is adherent to the wall and scars are present in the myocardium which appear to be the result of small infarctions. In these areas eosinophils are abundant.

Spleen. The pulp is crowded with eosinophils which to a lesser extent are invading the Malpighian follicles. They are for the most part adult polymorphonuclear cells, but myelocytes are frequently found. The eosinophilic granules appear normal but frequently, especially in the myelocytes, are sparsely scattered in the clear blue cytoplasm. Large cells resembling myeloblasts occur.

Liver. In the dilated sinusoids are many eosinophils whose morphology is similar to those encountered in the spleen. Here also are found a few large cells resembling myeloblasts. Many of the portal spaces are infiltrated with lymphoid cells and eosinophils.

Lymph Nodes. Eosinophils are more abundant in some nodes than in others. They are most frequent in the medulla, less so in the lymph cords and rather rare in the peripheral sinuses. Here as in the spleen the cells are for the most part adult, yet myelocytes are frequent.

Bone Marrow. The bone marrow is very hyperplastic, the overwhelming majority of the cells being eosinophils in all stages of development. They are for the most part myelocytes. Megacaryocytes and myeloblasts are frequent.

The marked clinical resemblance of this case to pulmonary tuberculosis is interesting and apparently explained by the finding at autopsy of multiple hemorrhagic foci in the upper lobes of the lungs. The leukocytosis with enlarged spleen and moderate lymphadenop-

athy, together with the presence in several of the tissues of eosinophilic myelocytes, at once suggests that this condition may be a leukemia involving the eosinophilic system of cells. Yet, upon examining the blood smears one is struck by the maturity of the eosinophilic cells. It is difficult to find any that might be classified as myelocytes. One wonders if this is not rather an unusual response of the homopoietic system to some infective or toxic agent. A search through the literature yields reports of several cases rather strikingly similar to the present one and it seems probable that they all constitute a rare clinical entity.

The earliest similar case of which we are certain is that reported in 1912 by Stillman,[1] of a man complaining of vague pains and weakness who exhibited pallor, lymphadenopathy and splenomegaly. The white blood count ranged from 118,000 to 165,000 with 85 to 91 per cent eosinophils, 1.8 per cent of which were myelocytes. No parasites were found. The Wassermann reaction was positive. The patient was followed for only a month. The author classified the case as one of myeloid leukemia with predominance of the eosinophilic cells.

In 1919, Shapiro[2] reported the case of a diabetic, aged forty-eight years, who complained of weakness, cough and loss of weight and who had râles and dullness at the apices of the lungs, palpable epitrochlear and inguinal glands and an enlarged spleen. The white blood count rose from 15,600 to 236,000 with 48 to 86 per cent eosinophils and increasing numbers of myelocytes. The Wassermann reaction was 4+. No parasites were found. Autopsy showed no tuberculosis, but patches of pneumonia, a thrombus in the right ventricle and infarcts in the spleen. Microscopically, there was cellular conversion of the bone marrow with a predominance of eosinophilic myelocytes and myeloblasts and infiltration of the spleen, liver and lungs with eosinophilic cells. In this case also the author believed he was dealing with an eosinophilic leukemia.

In the same year Giffin[3] reported the case of a man, aged thirty-one years with marked splenomegaly, slight lymphadenopathy and a leukocytosis of 21,800, 73.6 per cent of which were eosinophils. Following splenectomy, the leukocyte count rose to 97,200 and later to 211,000 with eosinophils from 79 to 90.7 per cent almost all of which were mature forms. The patient died four and a half years later of empyema. The spleen and lymph glands showed many eosinophils and a few eosinophilic myelocytes. The bone marrow at autopsy was hyperplastic with many eosinophils, the majority of them well developed.

Aubertin and Giroux,[4] in 1921, reported the case of a cardiac who for the period of four years during which he was followed, showed a white count of 6900 to 26,000 with eosinophils up to 65.8 per cent, practically all of them adult cells. The spleen was slightly enlarged. No parasites were found and the Wassermann reaction was negative.

Death was due to heart failure. An autopsy was performed which, however, did not include microscopic study. They discuss the possible relationship of the condition to anoxemia.

In the following year McDonald and Shaw[5] reported the case of a man, aged forty-six years, whose history included loss of weight and some gastric disturbance. His spleen was enlarged and the leukocytes numbered 34,000 with eosinophils 71.4 per cent, only 0.7 per cent of which were myelocytes. Following splenectomy, the leukocyte count gradually rose to 138,250 with esoinophils 79.3 per cent, of which 4.7 per cent were myelocytes. During this period, there was apparent clinical improvement. The spleen showed the presence in the pulp and sinuses of eosinophils and esoinophilic myelocytes with, to a lesser extent, invasion of these cells into the Malpighian bodies. They cite a case seen by Dr. Edwin Matthew of Edinburgh, of a girl, aged twelve years, with digestive trouble and a leukocyte count of 12,000 to 15,000 with 85 per cent eosinophils. No parasites were found and the spleen was not felt. Unfortunately, the case could not be followed. Ward,[6] in commenting on the case described by McDonald and Shaw, tends to regard the eosinophilia as a response to some demand, and cites a number of earlier cases which he regards as similar. Perhaps chief among these is that reported by Malins[7] of a woman, aged thirty years, with painful splenomegaly. Following splenectomy, the leukocytes rose from 10,000 to 50,000 and large polymorphonuclear cells were found to be actively phagocyting red cells. There is, however, no apparent proof that these cells were eosinophils.

In 1923, Langen and Djamil[8] reported the case of an asthmatic, aged thirty years, with a total white count of 12,400, 75 per cent of which were eosinophils, apparently all adult cells. The spleen was not palpable on admission, but later was felt two fingers breadth below the costal margin. On one occasion a vermifuge yielded 33 ankylostoma. On a purin-free diet, the percentage of eosinophils dropped from 85 to 51 per cent, later rising again with the addition of purins to the diet. They classify their case as an idiopathic hypereosinophilia.

In 1925, Böekelmann[9] reported the case of a man previously infected with malaria and hookworm, who complained of dizziness, dyspnea, cough and hemoptysis. He had fever, hypertension and albuminuria. The leukocytes numbered 36,400 with 74.8 per cent eosinophils. The spleen was considerably enlarged. Searches for parasites yielded only trichocephalus dispar in the stool on one occasion. After six month's treatment with a purin-free diet, the patient was symptom-free, the spleen was no longer felt and the white blood count was 7040 with 15 per cent eosinophils.

The same year Schmidt and Weyland[10] reported a case of acute fatal illness characterized by diarrhea, stiffness of the extremities, muscle pains and high fever. The total white blood count was

90,000 with 67 per cent eosinophils, all adult forms. The spleen was not felt. At autopsy small thrombotic vegetations were found on the mitral valve and also thrombosis of some of the smaller coronary arteries. The spleen was not enlarged, but showed a hyperplastic pulp filled with eosinophils. Many eosinophils were present in the interlobular stroma of the liver. The walls of the intestinal ulcers contained round cells and eosinophils. The histology of the lymph nodes suggested leukemia except that the eosinophils were adult forms. In the bone marrow the young forms were only slightly increased.

The same year, Bass[11] reported the case of a child, aged six years, who had been referred to him for examination prior to a sinus operation. She had been known to have an enlarged spleen at the age of two years. At the time of examination she was found to have moderate lymphadenopathy with enlarged spleen and liver. The white blood cells numbered 14,800 to 25,600, with adult eosinophils 37 to 64 per cent and eosinophilic myelocytes up to 6.3 per cent. No parasites were found. Soon after the child died of bronchopneumonia. An autopsy was not performed.

In 1927, P. Armand-Delille and Pierredon[12] reported the case of a child, aged thirteen years, who, for the five months during which it was observed, had a leukocytosis of about 35,000 with an eosinophilia of 76 per cent. The child had had malaria with a number of recurrences and at the time of observation was suffering from severe bronchial asthma. There was some cervical adenopathy and the spleen was felt three fingers below the costal margin.

Hodgkins disease may produce a somewhat similar picture. Krumbhaar[13] reports a case in a young woman, aged twenty-eight years, with a rapidly fatal febrile course, where the leukocytes rose to 120,000 with as high as 90 per cent mature eosinophils and the bone marrow loaded with eosinophils.

It is difficult to say whether some of these cases should be classified as a true leukemia or as a hyperleukocytosis, but it seems likely that they, together with the case reported here, constitute a clinical entity having the following features:

1. Leukocytosis of varying degree with a very high percentage of eosinophils, practically all of which are adult forms.
2. Splenomegaly and a moderate degree of lymphadenopathy.
3. Following splenectomy a marked increase of the eosinophilia without, however, any corresponding change in the clinical appearance of the patient.
4. Apparently a decreased resistance to infection, so that death supervenes from intercurrent disease after a variable period of time.
5. At autopsy a hyperplastic bone marrow filled with eosinophils in all stages of development, and in the spleen and lymph glands not only large numbers of adult eosinophils, but also a few eosinophilic myelocytes.

Summary. 1. A case is reported with marked eosinophilia and an enlarged spleen. No parasites were found. Autopsy revealed a hyperplastic bone marrow filled with eosinophils and in the spleen and lymph nodes very many eosinophils and occasional eosinophilic myelocytes.

2. Similar cases are reported from the literature.

3. The belief is expressed that these cases constitute a clinical entity.

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DEPRESSED BONE-MARROW FUNCTION FROM THE ARSPHENAMINS.

(Including a Type of So-called Agranulocytosis.)

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The condition, instanced by the following case histories, is comparatively rare. For some reason not well understood, no accounts of it are found before the year 1919, despite the fact that salvarsan was brought out by Ehrlich in 1910 and neosalvarsan in 1912. Labbe and Langlois (1919) first described this complication of arsphenamin treatment. I have found reports of 39 cases since then. Of these, 23 patients died and 16 recovered.

Case Reports. Case I.—M. C., a female, aged thirty-three years, was admitted on January 25, 1925, because of vaginal bleeding. She had had 6 intravenous injections of neoarsphenamin and 8 mercurial injections. The dates of injections were:

Date.	Neoarsphenamin, gm.	Date.	Mercury salicylate, gm.
June 4, 1924	0.6	July 23, 1924	1
June 8	0.6	Sept. 24	1
June 25	0.6	Oct. 1	1
July 2	0.6	Oct. 8	1
July 9	0.6	Oct. 22	1
July 16	0.6	Oct. 29	1
		Nov. 12	1
		Nov. 19	1

After the last mercurial injection, her gums became sore. At the time of admission, the gums were bleeding freely. On December 20, she began to bleed from the vagina. This had continued since with fever, fainting spells, weakness, headache, and bleeding from the nose. Her appetite had been poor. She had had no hematemesis. She had been constipated. She had not bled from the bowels. Shortness of breath and palpitation of the heart were present. She thought she had become more anemic. Her menstrual periods had always been regular and of normal duration. She stated that she contracted syphilis from her husband sixteen years before. She had six children.

Examination. Marked pallor, cyanosis of the lips, normal pupillary reactions and elevated temperature were noted. The gums were slowly oozing blood. Pyorrhea and many gold-capped teeth were present. One small posterior cervical lymph node was felt. The examination of the lungs and heart gave negative signs. The spleen was not felt. The lower edge of the liver was 3 cm. below the rib margin in the midclavicular line. The peripheral reflexes were hyperactive. There was no swelling of the legs. Vaginal examination was negative except for oozing of blood from the cervix.

Progress. January 31. The uterus was curetted and packed with thromboplastin-soaked gauze.

February 1. A blood transfusion of 200 cc. was done.

February 2: The patient was very weak and extremely anemic. This note was made: "Yesterday, there was oozing of blood from the gums. Today, bleeding from the gums and vagina has ceased. There is no purpuric eruption. There are no signs of local disease to account for patient's condition. There is a marked leukopenia affecting mainly the polymorphonuclear cells. She has the signs and symptoms of aplastic anemia. There is increase in the bleeding time and reduction in the blood platelets. There is no jaundice or other gross evidence of blood destruction."

February 4: Elevation of temperature continued. The patient was semistuporous. There was no further bleeding from the gums or vagina.

February 5: The patient had a chill and was very weak and stuporous. The packing was removed from the vagina. This was followed by a slight hemorrhage.

February 7. A transfusion of 325 cc. of blood was done. The patient grew progressively worse, despite this, and died on this date.

Laboratory Notes. Average Urine Analysis: Color, amber; reaction, acid; specific gravity, 1030; albumin, none; sugar, none; no pus; no red blood cells.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Lymph., per cent.	Myelo., per cent.
Jan. 26, 1925 . .	10	870,000	3200	22	78*	1
Jan. 31 . .	10	530,000	2900			
Feb. 2 . .	10	560,000	2800	12	88*	0

* The lymphocytes were small lymphocytes of normal morphology. No nucleated red cells were found.

Blood Platelets. February 2, 1925: 89,600 per c.mm.

Bleeding Time. February 2, 1925: thirty minutes.

Wassermann Test. The Wassermann reaction was moderately positive.

Comment, Case I. If we had been ignorant of the arsphenamin treatment this patient had received, we might have diagnosed her condition as acute idiopathic purpura hemorrhagica, because of the general picture, the thrombocytopenia, the prolonged bleeding time, and so forth. It is to be noted that she received no neoarsphenamin for four months before the onset of symptoms. However, she received mercurial injections at weekly intervals after her last injection of neoarsphenamin. It is well known that mercury is also to some degree a bone-marrow depressant. The anemia was initiated by blood loss from hemorrhage. The paralyzed or destroyed erythroblastic tissue no doubt failed to produce red cells to replace the loss. We have evidence sufficient in this case to say that an aplasia (physiologic at least) of the myeloblasts, the erythroblasts, and the megakaryocytes was present.

CASE II.—N. T., a male, laborer, white, aged thirty-three years, was admitted on August 3, 1925. His complaints were soreness of the mouth, eruption of the skin, fever and general weakness. He had been treated for syphilis by weekly intravenous injections of neoarsphenamin for six weeks. On July 20, 1925, after his fifth injection, he had swelling and tenderness of the gums, a papular eruption of the face with swelling and redness of the right eyelid. These symptoms were disregarded by his physician; no blood count was made, and a sixth and last injection of neoarsphenamin was given on July 29, 1925. After this, he felt feverish and very ill. The soreness of the mouth increased. He was admitted to the Medical Ward four days later.

Examination showed a young man acutely ill with fever, appearing moderately prostrated and without pallor or edema. A papular eruption was seen over the face and anterior chest. A blepharitis of the right eye with congestion of the conjunctiva was noted. The right pupil was slightly smaller than the left. The gums were swollen, red and tender. The lungs seemed normal. A faint systolic murmur was heard at the apex of the heart. The liver, spleen and kidneys were not felt. There was no lymphadenopathy. A tentative diagnosis of arsenical stomatitis, dermatitis and blepharitis was made. The patient was given sodium thiosulphate intravenously without improvement.

Progress. August 9: The patient was acutely ill. A few fine râles were heard at the base of the right lung.

August 10: The patient was slightly jaundiced. The liver dullness extended 18 to 30 cm. below the costal margin in the midclavicular line. An ischiorectal abscess was found. A possible septicemia was thought of.

August 11: The ischiorectal abscess was incised. Cellulitis about the sacrum was seen. Jaundice was increased. The liver was tender. Râles at the right base and the left apex of the lung were noted with prolonged expiration.

August 14: The pulse became weaker, respirations forced, jaundice deeper, and the patient died at 8 P.M. The patient's temperature was constantly elevated throughout his illness.

Laboratory Reports. Urine: The specific gravity varied from 1010 to 1024; albumin varied from a slight tract to a cloud. Many dark, granular casts were present.

Blood Counts. Hemoglobin, 73 per cent; red blood cells, 3,900,000 per c.mm.; leukocytes, 1000 per c.mm.

Differential Blood Count. Polymorphonuclear, 0; lymphocytes, 100 per cent; transitionals, 0; eosinophils, 0. The lymphocytes were of normal morphology. No nucleated red cells were seen.

August 9: The total leukocyte count was 3600 per c.mm., of these, 26 per cent were polymorphonuclears, 70 per cent lymphocytes, and 4 per cent transitionals. The lymphocytes were of normal morphology. No nucleated red cells were seen.

Blood Chemistry. August 9: Urea nitrogen, 92; creatinine, 9.5; sugar, 104 mg. per 100 cc.

Blood Culture. August 9: Bacillus proteus was isolated.

Necropsy. (Dr. John R. Paul.) There was marked jaundice of the skin, conjunctivæ, and all the internal organs. An area of cellulitis was present in the region of the buttock.

The liver weighed 2240 gm. The liver cells were greatly vacuolated, chiefly about the central vein of the lobule.

The spleen weighed 450 gm. The Malpighian corpuscles were well defined. Small hemorrhages were scattered throughout and many polymorphonuclear cells were present.

The heart showed only parenchymatous changes on microscopic examination, but no gross lesion. The pleuræ showed no lesions. The lungs showed passive congestion at the bases. Many alveoli were partly collapsed. A few contained blood and fibrin, but there was no inflammatory reaction.

The stomach, ileum and colon showed hemorrhagic gastritis, ileitis and colitis.

Parenchymatous changes were present in the kidneys and the adrenals.

The postmortem blood-urea nitrogen was 160 mg. per 100 cc. of blood. Postmortem blood culture gave the proteus bacillus in pure culture. The bone marrow was not examined. No enlargement of lymph nodes was found in any of the superficial or deep groups.

The anatomic diagnoses were: Diffuse papular dermatitis with ulceration and gangrene of buttock, bacteremia with bacillus proteus, hemorrhagic bronchopneumonia, hemorrhagic gastritis, ileitis, and colitis, and acute parenchymatous degeneration of the liver and kidneys.

Comment, Case II. This patient's bone marrow was apparently destroyed or paralyzed by neoarsphenamin. A profund reduction in the output of polymorphonuclear leukocytes occurred. His natural immunity against infection was seriously impaired. A septicemia by bacillus proteus, an organism usually nonpathogenic, followed. The organisms of the mouth cavity invaded his tissues. The patient had symptoms at least a week before his last injection which should have led his physician to investigate his blood picture. Some reduction in the differential percentage of granular cells no doubt existed at that time.

CASE III.—L. M., a colored female, aged twenty-three years, was admitted on August 29, 1924, complaining of sore mouth, sore throat and headache. The soreness of the mouth began four days before. There were marked salivation and painful gums, but no bleeding. Fever and anorexia with vomiting of all food, frontal headache, burning and redness of eyes were noted. She had several watery stools in the twenty-four hours before admission. The diarrhea ceased soon after admission. The previous medical history, family and social history were unimportant.

Since January, 1924, her menses had been profuse and prolonged (two to three weeks) and accompanied by backache. In July, 1924, she had been on our surgical wards because of uterine bleeding. Clinical examination at that time was negative and a diagnostic curettage was done. No radiotherapy was used. The report on the uterine scrapings was hypertrophic endometritis. The bleeding ceased. Her Wassermann reaction was found to

be strongly positive. She received 0.3 gm. of neoarsphenamin on August 16 and August 23, respectively. She was sick all week after the second injection (August 16, 1924) and the third injection made her much worse, marking the onset of the present illness.

Examination (on admission) showed a temperature of 103° F., a pulse of 124 and respirations of 36. There was jaundice of the scleræ and salivation. The gums and the oral mucosa were red, swollen and tender. The pharynx was injected. Slight cervical and epitrochlear adenopathy was noted. The heart and lungs were negative. The liver was enlarged and tender. The spleen was just palpable.

She was menstruating at the time of admission. She developed small ulcerations in the mouth (roof and left cheek) and several teeth became loose and were extracted as well as a piece of necrotic mandible. The temperature became normal September 15 after a typhoid-like course and a decline by lysis.

Laboratory Reports. Urine: The urine showed a trace of albumin and occasional hyaline casts.

Wassermann Test. The blood Wassermann reaction was strongly positive.

Blood Count. The blood counts were as follows:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Lymph., per cent.	Mono., per cent.	Myelo., per cent.
Aug. 29, 1924	55	3,300,000	5250	0	100	0	0
Sept. 1	..	...	3350	1	24	4	69
(Oxidase stain; granular cells, 64 per cent; nongranular cells, 36 per cent.)							
Sept. 12	55	...	5800	16	58	0	26
Sept. 20	65	...	6200	33	44	0	21
Sept. 27	..	...	9050	44	46	0	10
Oct. 8	..	...	6600	56	43	1	0

After an uneventful convalescence, she was discharged free of symptoms on October 14, 1924, after which she was seen in the medical dispensary, and also in the salvarsan clinic on the following dates:

November 1, 1924: She received neosalvarsan 0.3 gm. intravenously.

November 11, 1924: She felt well, although menstruating every two weeks but not excessively. The blood showed: Hemoglobin, 85 per cent; red blood cells, 4,440,000, leukocytes, 6800, neutrophils, 55 per cent; mononuclears, 5 per cent; lymphocytes, 37 per cent; eosinophils, 2 per cent; basophils, 1 per cent.

December 6, 1924: She was free of symptoms. The blood showed: Hemoglobin, 80 per cent; polymorphonuclears, 47 per cent; small lymphocytes, 36 per cent; large lymphocytes, 12 per cent; mononuclears, 4 per cent; eosinophils, 1 per cent.

December 17, 1924: She was given neosalvarsan 0.3 gm. intravenously.

January 15, 1925: She was feeling well but had a chill and felt badly for several days after the last dose of neosalvarsan. The blood showed: Leukocytes, 7200; neutrophils, 45 per cent; small lymphocytes, 49 per cent; large lymphocytes, 6 per cent.

January 22, 1925: She was feeling quite well. No blood count was made and she never returned and could not be located thereafter.

Comment, Case III. Although this patient had received no mercury, she had the general appearance of mercurial salivation. The prominent features were the swollen mucous membrane of the mouth with constant profuse dribbling of saliva, the depressed state

of the polymorphonuclear cells, and the constantly elevated temperature. It is questionable whether further arsphenamin therapy should have been attempted so soon after her severe illness. The danger of a further acute depression of the bone marrow even by small doses of arsphenamin was great. The presence of large numbers of myelocytes was interpreted as a stimulation myelocytosis.

CASE IV.—J. C., a white male teamster, aged nineteen years, was admitted on June 30, 1927, complaining of weakness and fever. He was well until February, 1927, when he had a chancre. Following this, he was given three intravenous arsphenamin treatments by his family physician. The exact date and dosage of this medication are unknown to me. There were no ill effects at the time of injection. He had no secondary syphilitic manifestations and felt well until April, 1927, when he developed quinsy on the left side. This was treated by incision and several days' rest in bed. The throat condition became well, but since this time (two months) he had not worked because of progressive weakness, fever, increasing pallor and chilly sensations. He had had no hemorrhages at any time. The past history was negative except for chancre as noted. The family and social history were negative.

Examination. This showed a well-developed young man markedly pale and quite toxic in general appearance. There was a generalized lymphadenopathy of slight degree. Nothing abnormal about the head was noted except cryptic tonsils. The lungs were apparently normal. The heart was enlarged. Systolic and diastolic basal murmurs and a Corrigan pulse were present. The spleen and liver were barely palpable. A tentative diagnosis of acute endocarditis was made before the blood picture was known.

Course. A typhoid-like temperature persisted until death occurred three weeks after admission. Blood cultures taken on June 30 and July 6, 1927, were sterile. A blood culture on July 18 was positive for Bacillus pyocyaneus. On July 2, a small bloodclot was expectorated. This was the only hemorrhagic feature. He showed no purpuric lesions during his course. The margins of the gums were infected and edematous but did not bleed.

Treatment. Blood transfusions were done on July 7 and 12, 1927. The transfusions did not improve his condition. Intravenous injections of tartar emetic (10 cc. of a 1 per cent solution) were given July 8, 9, 10, 12 and 15, 1927. No effect, good or bad, was noted. The patient died of toxemia on July 21, 1927. No necropsy was obtained.

Laboratory Reports. Urine: Urine analyses were negative.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Lymph., per cent.	Blood platelets, per c.mm.
July 1, 1927 . . .	30	900,000	30,000	100	
July 5 . . .	20	950,000	52,300	100	270,000
July 8	30	1,160,000	(After transfusion, 24 hours)		
July 10 . . .	...	1,075,000	59,200	...	300,000
July 13 . . .	30	1,503,000	42,000	100	
July 19 . . .	25	1,503,000	60,000		

Oxidase stains failed to show granules in the mononuclear cells. Blood platelets on July 5, 1927, were 270,000 per c.mm., on July 10, 300,000 per c.mm.

Wassermann Test. The Wassermann reaction was strongly positive.

Comment, Case IV. The absolute absence of granular cells and the increase in lymphocytes is to be noted. Immunity was lowered to such a degree that the saprophyte, Bacillus pyocyaneus, gained entrance to the blood stream. It seems likely that this patient died from acute lymphatic leukemia. The influence of his arsphenamin injections from the point of view of etiology is problematical. The injection may have been merely coincidental. When the cause of acute lymphatic leukemia is fully understood, the connection may become clear. The literature records two cases similar from the point of view of great increase in leukocytes. Vill (1921) published reports of two young women who had received intravenous injections of collargol after preceding injections of neoarsphenamin. Both died from acute intoxication with hemorrhages, thrombocytopenia and purpura. In one patient there was a leukocyte count of 76,000, in the other 29,000 per c.mm. Vill considered the condition due to the selective action of silver on the reticuloendothelial system. Herzog and Roscher (1922) reported special studies on the same cases and arrived also at the conclusion that the condition was due to collargol poisoning.

Case V.—M. H., a colored male, aged twenty-two years, admitted March 2, 1928, complaining of epigastric pain and jaundice. In September, 1927, he had a chancre. In April, 1928, he developed a secondary syphilitic skin eruption. He had no specific treatment until this time. Two weeks after the appearance of the eruption, he received his first dose of neoarsphenamin. He received injections of mercury and neoarsphenamin between this time and October 23, 1928, as follows:

Date.	Dose, cc.	
April 4, 1928	10.0	Mercodel.
April 8	0.6	Neoarsphenamin.
April 11	10.0	Mercodel.
April 13	0.6	Neoarsphenamin.
April 18	10.0	Mercodel.
April 20	0.6	Neoarsphenamin
April 25	10.0	Mercodel.
April 27	0.6	Neoarsphenamin.
May 2	10.0	Mercodel.
May 9	10.0	Mercodel.
May 11	0.6	Neoarsphenamin.
May 16	10.0	Mercodel.
May 18	0.6	Neoarsphenamin.
May 23	10.0	Mercodel.
May 25	1.0	Mercury salicylate.
June 6	10.0	Mercodel.
July 11	0.6	Neoarsphenamin.
July 18	0.6	Neoarsphenamin.
July 25	0.6	Neoarsphenamin.
Aug. 1	0.6	Neoarsphenamin.
Aug. 8	0.6	Neoarsphenamin.
Aug. 15	0.6	Neoarsphenamin.
Aug. 22	10.0	Mercodel.
Sept. 12	10.0	Mercodel.
Sept. 26	10.0	Mercodel.
Oct. 3	10.0	Mercodel.
Oct. 10	10.0	Mercodel.
Oct. 17	10.0	Mercodel.
Oct. 24	10.0	Mercodel.

One week after the last injection, he became jaundiced and suffered from vague epigastric pains, most intense three or four hours after meals and radiating along the left rib margin to the back. There was no vomiting. His urine was dark and smoky. His best weight had been 163 pounds. His admission weight was 140 pounds. There was no family history of blood dyscrasia. He had had measles and chicken pox in childhood, but had since been well.

Examination. Blood pressure: Systolic, 110; diastolic, 70. Pulse and temperature were normal. He was a well-developed young adult negro, aged twenty-two years. He did not seem to be very sick. There was deep jaundice of the scleræ. The pupils were equal and reacted normally. The nose was negative. The mouth cavity showed no abnormality except questionably diseased tonsils and two carious teeth. There was no thyroid enlargement and no cervical adenopathy. Examination of the lungs showed normal findings. Examination of the heart showed no abnormalities except a soft systolic apical murmur. There was slight epigastric tenderness. The liver, spleen and kidneys were not enlarged. The epitrochlear and inguinal lymph nodes were slightly enlarged. The peripheral reflexes were normal. There was no edema.

Laboratory Examinations. Wassermann Test: The Wassermann blood test was strongly positive.

Urine Examination. The urine contained an excessive amount of bile.

Stool Examination. Bile was present. No ova nor parasites were seen.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Eosin., per cent.	Bas., per cent.	Lymph., per cent.	Mono., per cent.	Trans., per cent.
Nov. 11, 1928	97	4,450,000	4100	30	none	none	69	none	1
Nov. 30	..	....	9900	46	5	1	41	4	3
Dec. 7	..	....	6300	68	2	none	26	4	none

Course in Hospital. The patient was treated by rest in bed, general care and duodenal drainage. The jaundice cleared up rapidly. His general condition improved. He was discharged apparently in good health on December 8, 1928.

Discussion. This patient had an hepatitis precipitated by his antiluetic treatment. He also had undoubtedly a mild depression of his bone-marrow function. If he had received an additional dose of arsphenamin, I believe that he would have died from bone-marrow depression.

CASE VI.—K. C., a female, aged forty-four years, had a pelvic operation at the Frankford Hospital in March, 1928. At this time, she was found to have a positive blood Wassermann test, and was given intravenous injections of neoarsphenamin. The exact number of injections is not known. On July 27, 1928, she was transferred for further antisyphilitic treatment to the Outpatient Department of the Pennsylvania Hospital. She received intravenously 6 doses of neoarsphenamin, each dose being 0.6 gm., and the interval between doses a week. She was then given 12 intramuscular

injections of bichlorodol at weekly intervals. She then had a month's rest from treatment. On December 26, 1928, she was given 0.6 gm. of neoarsphenamin. On January 2, 1929, she complained of not feeling well. Her symptoms, however, were not definite enough to be disturbing, and she was given an injection of 0.6 gm. of neoarsphenamin intravenously, and 10 grains of sodium thiosulphate four times a day by mouth. On January 9, 1929, another injection of 0.6 gm. of neoarsphenamin was given.

About an hour after this injection, she began to bleed from the gums. She bled rather profusely for about eighteen hours, when the bleeding ceased. She "hawked up" a considerable amount of blood. At the same time, there was diarrhea with bloody bowel movements. She was prostrated and suffered especially from backaches. Her family physician who examined her at the time stated that she had a great many purpuric spots all over the body and that she lost such a large amount of blood that she was "bled white." The patient was so sick that she was afraid she would die. Her physician thought she would die from blood loss. She failed to report her condition to the Clinic; therefore, she was not followed until February 2, 1929. At this time, she seemed to have completely recovered and was doing her housework. A blood count was made on February 2, 1929, as follows: Hemoglobin, 65 per cent; red blood cells, 3,280,000; leukocytes, 6600; polymorphonuclears, 69 per cent; lymphocytes, 23 per cent; monocytes, 7 per cent; basophils, 0; eosinophils, 1 per cent.

The patient refused to return to Clinic for treatment.

Comment, Case VI. It is unfortunate that it was impossible to get blood counts on this patient until almost a month after the occurrence of hemorrhagic symptoms. The hemorrhages, the purpuric eruptions and prostration make it highly probable that there was a temporary depression of the bone marrow, affecting especially the blood platelets, with secondary hemorrhages from the mucous membranes.

The following case, with others showing leukemoid blood pictures in various clinical conditions, has been previously reported by Dr. E. B. Krumbhaar (1926). Through the courtesy of Dr. Krumbhaar it is included here in order that it may be more accessible as an instance of the rather rare condition under discussion.

CASE VII.—"Ha. I., a young married woman, aged twenty-one years, was admitted to the Philadelphia General Hospital, December 29, 1925, with acute gonorrhea and syphilis, both of which diagnoses were amply confirmed by history, examination and laboratory findings. Except for a slight general adenopathy and two carious teeth, there was nothing apparently germane to the present study.

"One month later, while her treatment was progressing satisfactorily (she had received a series of from 8 to 10 neoarsphenamin injections—Dr. H. F. Kotzen) her temperature, which had been practically normal, suddenly jumped to 102° F., and stayed rather constantly between 102° and 104° F. for nine days. A superficial ulceration was noted on the gums, which spread during the week and repeatedly yielded smears of Vincent's organisms (though not considered in every way typical). The submaxillary and submental nodes became slightly more enlarged, but the spleen was never palpable. On the eleventh day, the patient never having been more than slightly discommoded, except by the mouth ulcers, the temperature dropped quickly to normal, the ulcers soon healed and the patient has continued well ever since.

"Blood examination on the first day of fever showed a leukocyte count of 15,200, of which only 8 per cent were polymorphonuclears, 48 per cent lymphocytes and 44 per cent were doubtful large mononuclear cells which were eventually considered to be myelocytes. The next day the count had dropped to 4700 leukocytes with 60 per cent of the doubtful cells, and during the remainder of the illness the count remained between 3300 and 5600, distributed in a similar manner. On the day on which the temperature dropped, the count rose to 6300 and by the next day the special cells had practically disappeared. Although they reappeared later in small numbers, the leukocyte count remained about 6000 and the patient perfectly well until two months later March 28, 1926, when she eloped from the hospital.

"*Blood Counts:*

Date.	W. b. c., per cent.	Polymor., per cent.	Lymph., per cent.	Mono., per cent.	Eosin., per cent.	Bas., per cent.	Rieder cells, per cent.	Myelobl., per cent.	Myelocy., per cent.	Meta., per cent.	Hb., per cent.	R. b. c., per c.mm.
Feb. 2, 1926	15,200	8.0	48.0	..	..	..	..	..	44			
Feb. 3	4,700	5.0	35.0	..	..	..	..	..	60	..	60	3,700,000
Feb. 5	4,700	6.0	41.0	..	..	..	..	..	53	..	63	3,550,000
Feb. 6	3,900	4.0	49.0	..	..	..	..	..	47			
Feb. 7	5,600	1.0	52.0	3	..	..	..	..	44			
Feb. 8	4,000	0.5	61.5	3	..	..	..	1	34			
Feb. 9	3,300											
Feb. 10	4,000	..	..	..	..	..	..	..	..	..	66	4,030,000
Feb. 11	6,300	32.0	55.0	..	..	..	..	..	13			
Feb. 12	6,000	44.0	47.0	..	1	..	7	..	1			
Feb. 13	6,800	40.0	60.0									
Feb. 15	6,900	49.0	46.0	2	2	1	..	..	..	..	98	4,600,000
Feb. 16	6,100	59.0	39.0	..	1	1						
Feb. 18	6,200	52.0	47.0	1								
Feb. 22	8,000	65.0	28.0	5								
Mar. 5	5,500	56.0	23.0	5	7	..	6	..	..	2	70	3,400,000
Mar. 12	5,300	40.0	44.0	2	3	1	..	..	..	..	80	

Comment, Case VII.—"A blood sample taken during the height of the illness was shown to an unusually competent hematologist, who, on the basis of the blood picture coupled with fever and mouth ulcers, was strongly in favor of a diagnosis of acute leukemia. Subsequent clinical and hematologic developments, however, fairly rule this out."

General Discussion. The cases here reported belong to the group of symptomatic blood dyscrasias resulting from known causes. Benzol, radium and the Roentgen ray in excessive dosage may produce similar clinical pictures. Selling (1910) first called attention to the peculiar selective depressant action of benzol on the hemopoietic apparatus. The fact that benzol has such an action is of special interest when it is remembered that the arsphenamins are formed by the substitution of arsenic about the benzol ring.

It seems likely that arsenic is not the offending substance since arsenic poisoning does not usually produce a picture like that of the

group under discussion. However, a case of so-called granulocytic aplasia of the bone marrow following the use of an inorganic arsenic compound has recently been reported (1928) by Dr. Robert Y. Wheelihan, which seems of special interest in this connection. A child, aged nine years, with generalized involuntary twitching present since one month old, and thought to be caused by cerebral injury at birth, was given a total of 625 minims of potassium arsenate (0.41 gm. or 6 grains of arsenic trioxid) over a period of thirty days. She developed fever, inflammation of the pharynx, gingivitis and infected teeth. The liver, spleen and submaxillary lymph nodes were enlarged. The white blood cell count dropped from 14,400 to 1300 cells, with a decrease in the polynuclear neutrophils from 62 to 3 per cent, and a corresponding increase in the lymphocytes from 34 to 93 per cent. On the seventh day following onset of fever the temperature became normal, the white cell count rose to 8450 with 52 per cent neutrophils. The child recovered. Wheelihan states that this is apparently the first case on record with marked changes in the blood picture due to inorganic arsenic as such.

Recently, we have treated an unusually severe case of arsenic poisoning, a child aged nine years who had been given arsenic for ten consecutive months with resulting general edema, secondary anemia, wrist and toe drop. This patient had no depression of polymorphonuclear cells, no lowering of blood platelets, no hemorrhages, or other particular symptoms, found in these cases.

In the literature there are reports of blood dyscrasias following arsphenamin treatment under a variety of titles, aplastic anemia, purpura hemorrhagica, bone-marrow depression, agranulocytic angina, and so forth. All of these symptomatic depressions of bone marrow occur, dependent, no doubt, upon the degree of toxic action and the particular elements of the marrow suffering most injury. A general term, such as, "depressed bone-marrow function" seems desirable.

The condition is a rare one. During the past seven years, only 6 cases have occurred at the Pennsylvania Hospital. Coombes (1927) reports one case after four thousand injections of the arsphenamins. The condition does not seem to be due to unusual toxicity of a particular batch of the drug since it does not affect more than one individual, where many are receiving treatment from the same solution. It is possible that those individuals in whom depression of the marrow occurs possess congenitally, a weak hemopoietic apparatus. No proof can be found to directly support this. It seems probable that a depressed state of the marrow which also depressed natural immunity may exist for some time without symptoms until a chance infection reveals the situation. Secondary infection, no doubt, plays a large part in the destruction of the patient.

Reported cases indicate that no one type of arsphenamin is more apt to produce depression than another. Arsphenamin, neoarsphenamin, novarsenbenzol, sulpharsphenamin, silver arsphenamin seem to be equally potent in this regard.

A knowledge of the prodromal symptoms of acute aplastic anemia is of especial importance since the withholding of an injection of arsphenamin in a patient who has begun to show signs of bone-marrow depression, may save the patient's life. The mortality of the condition is very high after the symptoms become pronounced. A blood count, of course, is the most accurate check on the patient's condition, so that one who uses arsphenamin should know when to have a blood count made. Data on prodromal symptoms is scanty. Moore and Keidel (1921) state that itching, a mild macular, papular, or vesicular rash, prolonged fever or malaise, or any tendency towards purpura in a patient who has received arsphenamin, indicate that a blood count should be made before proceeding with the treatment. They also found an increase in eosinophils of from 5 to 8 per cent a warning sign. A slight decrease in the neutrophils is especially ominous. After a patient has shown symptoms of possible depressed bone marrow a long interval should elapse before further injections are made. No one knows how long this interval should be. A safe interval of time might be placed at a year, because of the extreme danger. Every patient who shows jaundice or unusual symptoms of any kind after arsphenamin medication, should have a blood examination before proceeding to the next injection.

The symptoms and signs of poisoning can be predicted from our knowledge of the pathologic physiology of the marrow. The arsphenamins do not always depress equally the various elements of the hemopoietic apparatus. Thus certain ones may fail to have hemorrhagic purpuric symptoms because the blood platelets have escaped, while at the same time there may be a profound anemia from the effect on the erythroblastic tissue. The lesion about the mouth and throat, and for that matter, inflammatory lesion elsewhere, such as bronchopneumonia, follow the destruction of the patient's active immunity. The exact site of origin of this immunity is unknown, but undoubtedly, ferments, originating in the polymorphonuclear cells, are an important part of it. When first seen, the patient's hemoglobin may be high and his blood platelets numerous. On the turn of the life cycle of the elements of the blood, the most desperate symptoms occur because the natural process of destruction of old and worn-out cells continues while the apparatus for supplying new cells has suddenly ceased to function.

While there is no specific treatment for acute anemia secondary to arsphenamin, there are certain logical indications for active therapy. Sodium thiosulphate may be given intravenously to attempt neutralization of remaining arsenic in the blood and tissues. This should be vigorously followed up and should be given as early as possible.

The lesions about the teeth and mouth should be treated by a dentist. Sodium perborate solution, 1 dram to a half glass of water used as a mouth wash is a very valuable solution.

Blood transfusions are indicated for the theoretical accomplishment of four objects of treatment: (*a*) To supply red blood cells and hemoglobin; (*b*) to supply polymorphonuclear cells; (*c*) to combat infection; (*d*) to supply soluble ferments probably decreased or absent from the patient's serum. Blood transfusions should be vigorously repeated. As many as 10 or 12 transfusions may be necessary, and this should be prepared for from the outset. It should constantly be kept in mind that the particular patient under treatment may not have an actual aplasia, but simply a temporary marrow depression, which stage may be tided over until the marrow is again able to supply the needed blood elements. One should not wait until the patient's condition is desperate to begin transfusions.

The most effective treatment no doubt is early recognition of the tendency to depression and the withholding of further antisyphilitic treatment until recovery of marrow function takes place.

Summary and Conclusions. Reports of seven cases of depressed bone-marrow function following arsphenamin treatment are detailed. The clinical pictures presented by these patients varied according to the degree of marrow depression and according to the particular element or elements of the marrow most affected. The cases reported belong to the group of symptomatic blood dyscrasias. It seems likely that the direct cause is disintegration *in vivo* of the arsphenamins, so that a benzol-like action takes place. This, however, is a matter of opinion and not of proved fact. The rarity of occurrence suggests a preceding weakness of the hemopoietic apparatus in the individuals affected. Careful blood examinations in patients showing unusual arsphenamin reactions should be made. Blood transfusions should be vigorously repeated in the treatment of bone-marrow depression, keeping constantly in mind that a physiologic paralysis rather than an actual aplasia may be present in the particular case, and that the patient may be tided over this phase to recovery.

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THREE ADDITIONAL CASES OF ACUTE HEMOLYTIC (INFECTIOUS) ANEMIA.

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In 1925, 3 cases of rapidly developing anemia of an hitherto undescribed type were reported by the writer.[1] As was stated in that article, no reference could be discovered in the literature to similar cases, although general mention of acute anemias of a hemolytic nature was found. Since that time, however, several articles have appeared which describe cases simulating those which occurred in the experience of the writer. I. C. Brill,[2] Steffens[3] and Benhamou, Jude and Gill[4] report cases under the title of "acute febrile anemia." Moschkowitz[5] describes a case of an "acute pleiochromic anemia, with hyaline thrombosis of the terminal arterioles and capillaries," and attempts to group it with those described by the writer. Comparison, however, fails to reveal the resemblance.

Holst[6] and Christiansen[7] report 2 typical cases. Holst believes that the disease bears no relationship to pernicious anemia. Christiansen's case did not respond to liver therapy and he quotes this fact as an additional argument against its relationship to pernicious anemia. This case recovered completely after long convalescence (two and a half months) without transfusion.

Since the last publication, the writer has had the opportunity to closely study 3 additional cases, and his attention has been called to 4 others. The 12 cases above mentioned presented similar clinical pictures and blood changes, and in 11 cases the disease was promptly arrested by transfusion. No sequelæ or fatalities occurred. The details of the 3 cases studied are as follows:

Case Reports. Case I.—M. S., (Hosp. No. 115366) male, aged twenty-four years, has always been well, except for an occasional cold. His color has always been good. His occupation is that of civil engineer. Three days before admission to the Jewish Hospital of Brooklyn, after returning from a vacation resort in the mountains, he became feverish, his temperature rising to 104,° and persisting between 103° and 104°. His appetite disappeared and he noted a rapidly increasing weakness. Two days later he began to vomit greenish material. On the day before admission his skin became yellow and the urine became red in color. The physical examination showed a well-developed and well-nourished young man who appeared weak, with a marked icteric tint and pallor to the skin and mucous membranes. His temperature was 102°, pulse rate 100, and respirations were 20. His mentality was clear. The scleræ were deeply jaundiced. There was noted a soft systolic murmur at the apex which was not transmitted. The spleen was palpable at the costal margin. Examination of

TABLE I.—THE BLOOD PICTURE OF CASE I.

Date.	Time.	Hemoglobin, per cent.	Erythrocytes, millions per c.mm.	Color index.	Platelets, per c.mm.	Leukocytes, per c.mm.	Differential study.											Red cell study.				
							Poly. neut., per cent.	Poly. eosin., per cent.	Poly. baso., per cent.	Small lymphocytes, per cent.	Türk cells.	Mononuclears.	Promyelocytes.	Myelocytes.	Metamyelocytes.	Per 100 W.B.C. Megaloblasts.	Per 100 W.B.C. Normoblasts.	Per 100 W.B.C. Free nuclei.	Anisocytosis and poikilocytosis.	Macrocytosis.	Microcytosis.	Stippling, per cent.	Reticulocytes, per cent.
8/16	9 A.M.	50	3.12	0.8	....	29,000	....	..	..	....	..	..	..	..	..	..	..	..	..	..	..	..	..
8/17	9 A.M.	35	2.24	0.8	....	....	....	..	..	....	..	..	..	..	..	..	..	..	..	..	..	..	..
	11 A.M.	21	1.13	0.8	140,000	44,000	60.0	..	..	27.0	..	7	..	1.0	..	1.0	8.0	Few	Marked	..	Mod.	..	8
	4 P.M.	30	1.02	1.5	....	....	....	..	..	....	..	....	..	....	..	....	....	....	Marked	..	....	..	....
8/18	9 A.M.	20	0.99	1.0	....	....	81.3	..	..	11.6	..	..	..	0.5	6.6	2.3	5.6	5.0	Mod.	..	Mkd.	0.6	....
	4 P.M.	33	1.20	1.4	....	....	....	..	..	....	..	....	..	....	..	....	....	....	....	..	....	..	....
8/19	....	35	....	..	....	....	77.5	..	..	13.5	..	2	1	1.5	4.0	3.0	1.5	7.0	Marked	..	Many	..	4
8/20	....	38	2.40	0.8	....	27,000	77.0	..	1	11.0	..	5	..	3.0	3.0	1.0	3.0	..	Marked	..	....	..	....
8/21	....	33	2.70	0.6	100,000	20,400	74.0	..	..	18.0	1	7	..	..	..	0.0	0.0	..	....	..	....	..	8
8/22	....	35	2.75	0.6																			
8/24	....	30	1.80	0.8																			
8/25	....	36	1.85	1.0	....	10,200	75.0	1	2	10.0	..	..	..	1.0	1.0	..	..	..	Mod.	..	Mod.	..	4
8/27	....	20	1.50	0.7	....	6,000	80.0	..	..	8.0	..	12	..	..	..	..	..	..	..	..	..	..	..
8/28	....	31	1.95	0.8	....	6,800	62.0	1	..	34.0	..	2	..	..	1.0	0.0	0.0	..	....	..	....	..	4
9/3	....	39	1.96	1.0	....	13,400	81.0	..	..	13.0	..	6											
9/5	....	37	1.64	1.1																			
9/7	....	45	1.84	1.3	....	10,800	79.0	..	..	12.0	..	9											
9/12	....	48	3.20	0.8																			
9/17	....	47	3.32	0.7	....	6,200	61.0	..	..	31.0	..	8											
9/20	....	46	2.98	0.8																			
9/25	....	56	2.59	1.1	240,000	5,800	50.0	4	..	38.0	..	6											
11/1	....	65	4.79	0.7	....	12,800	59.0	..	..	30.0	..	8	..	..	3.0	..	..	..	....	..	....	..	2

the blood showed a profound anemia, marked leukocytosis, and evidences of unusual hematopoietic activity. The details are noted in Table I. The urine contained a large amount of albumin and free hemoglobin, being of a thick, red, syrupy appearance. The course of the disease was very stormy. The anemia progressed at such an alarming rate that within twelve hours his hemoglobin fell from 35 to 21 per cent and his erythrocytes from 3,120,000 to 1,130,000 per cc. This was accompanied by an increase in the hemoglobinuria and jaundice. Fifteen hours after admission, a transfusion of 500 cc. of unmodified blood was given, with slight temporary improvement. The evidences of active blood destruction continued, and the patient became stuporous, the latter due probably mainly to uremia, and accenuated by cholemia and profound anemia. Two more transfusions of 500 cc. of unmodified blood were done on the next day, but the patient became worse and lapsed into complete coma. During this time his temperature declined. On the fourth day after admission, he began to emerge from the coma, but his blood continued to manifest evidences of renal insufficiency for about three weeks (Table II). Of special interest are the high-retention values of all the metabolites studied, except the chlorids. Because of the severe hemoglobinuria, urobilinogen and urobilin estimations could not be done. Great difficulty was also experienced in the quantitative estimation of bile pigments in the blood serum because of the high degree of hemoglobinemia. The icterus index on the day following admission was 48. By the van den Bergh method, the direct reaction for bilirubin could not be read because of the hemolysis. By the indirect method, however, 5.5 units were calculated; on August 20, the icterus index was 24. Van den Bergh estimations could not be made because of hemolysis. On the twenty-second, the icterus index had dropped to 20 and the van den Bergh showed a slight delayed positive direct reaction, the indirect method yielding 1.5 units. Comment on these figures at this time is not made excepting to emphasize the fact that the calculation of icterus index was of greater value than the van den Bergh reaction to recognize and estimate the bilirubinemia. He gradually improved, evidences of blood destruction disappeared, signs of regeneration became abundantly evident, and he gradually recovered completely. Reëxamination of the patient and his blood ten months later revealed no abnormality.

TABLE II.—BLOOD CHEMISTRY TABLE OF CASE I.

	Sugar, mg. per 100 cc.	Creatinine, mg.	Urea nitrogen, mg.	Uric acid, mg.	CO_2, volume per cent.	Chlorids, mg.	Diazo.
8/16	174	2.1	22.8	4.8	51.6		
8/18	272	....	....	....	59.4		
8/20	187	6.0	50.1	10.0	....	....	Neg.
8/22	150	10.0	50.0	10.0	....	....	
8/25	166	15.0	98.1	10.9	....	500	Pos.
8/27	166	15.0	80.4	10.8	....	500	Pos.
8/29	150	10.0	62.5	8.0			
8/31	150	6.0	83.3	7.5	....	....	Pos.
9/3	120	6.0	50.0	6.0			
9/10	103	3.5	31.2	6.6			
9/17	96	1.6	12.5	4.0			
9/20	100	1.7	13.1	4.3			

Case II.—P. V., male, aged three years. Excepting for pertussis at eight months of age, he has never been ill. Two days before admission to

TABLE III.—THE BLOOD PICTURE OF CASE II.

Date.	Hemoglobin, per cent.	Erythrocytes, millions per c.mm.	Color index.	Platelets, per c.mm.	Leukocytes, per c.mm.	Differential study.									Red cell study.								
						Poly. neut., per cent.	Poly. eosin., per cent.	Poly. baso., per cent.	Small lymphos., per cent.	Mononuclears, per cent.	Promyelocytes, per cent.	Metamyelocytes, per cent.	Myelocytes, per cent.	Anisocytosis and poikilocytosis.	Polychromasia.	Macrocytosis, per cent.	Microcytosis, per cent.	Stippling, per cent.	Megaloblasts, per 100 W.B.C.	Normoblasts, per 100 W.B.C.	Reticulocyte, per cent.	Howell-Jolly bodies.
3/9	10	1.07	0.5	....	39,600	77	..	..	21	2	..	..	..	....	....	Moderate	....	Mod.		[Few]		
3/10	30	2.12	0.7	280,000																		
3/11	34	3.00	0.6	260,000	38,000	45	1	..	40	11	3	..	..	Marked	....	....	....	....	..	..	10	Few
3/12	34	2.21	0.8																			
3/15	48	2.70	0.9																			
3/16	..	2.80	..	310,000																		
3/17	47	3.10	0.8	320,000																		
3/20	52	4.00	0.7	220,000	7,200	55	..	..	43	2				Slight								
3/21	52	4.02	0.7	300,000	6,500																	
3/29	51	4.30	0.6	240,000	5,600	60	..	..	39	1	..	..	..									
4/1	60	5.10	0.6																			
4/7	56	3.96	0.7	....	26,200	75	..	..	22	3												

the service of Dr. B. Kramer, he complained of abdominal cramplike pain and vomiting, the attack lasting several hours. This was accompanied by hemoglobinuria, and progressively increasing pallor. He appeared feverish (temperature 102.5°), drowsy and weak. Physical examination showed a well-developed and well-nourished child, with temperature of 102°, pulse rate 140 and normal respirations. The heart sounds were soft and rapid, and there was a soft systolic blow at the apex which was not transmitted. The tonsils were slightly enlarged but not congested. The abdomen was soft, the liver and spleen were not palpable. The blood picture is detailed in Table III and chart. The associated laboratory findings were as follows:

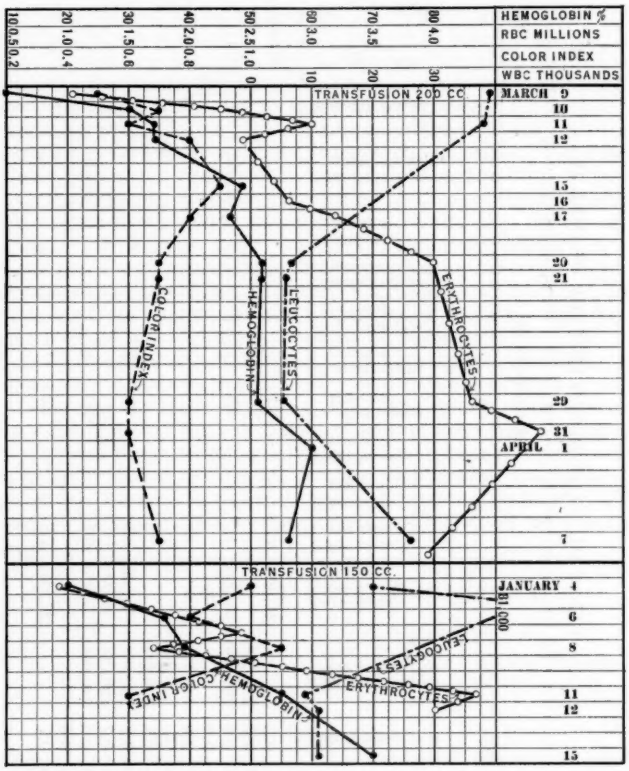

CHART.

bleeding time, 1.5 minutes; coagulation time, 3.5 minutes; platelet count, 300,000; tuberculin test was negative up to 5 mg. as was the Dick test; blood calcium, 10; phosphorus, 3; cholesterol, 236, and chlorids, 324 mg. per 100 cc. The blood Wassermann reaction was negative. The stools were negative for ova and parasites. As in the previous cases, on admission this case was one of marked anemia with evidences of pronounced bone-marrow activity. The urine contained large amount of hemoglobin. After a transfusion of 200 cc. of unmodified blood the hemoglobin rose from 10 to 34 per cent and the erythrocytes from 1,070,000 to 3,000,000 within a period of forty-eight hours. Within a week the hemoglobin disappeared

TABLE IV.—THE BLOOD PICTURE OF CASE III.

Date.	Hemoglobin, per cent.	Erythrocytes, millions per c.mm.	Color index.	Platelets, per c.mm.	Leukocytes, per c.mm.	Differential study.								Red cell study.								
						Poly. neut., per cent.	Poly. eosin., per cent.	Poly. baso., per cent.	Small lymphos., per cent.	Mononuclears, per cent.	Promyelocytes, per cent.	Metamyelocytes, per cent.	Myelocytes, per cent.	Anisocytosis and poikilocytosis.	Polychromasia.	Macrocytosis, per cent.	Microcytosis, per cent.	Stippling, per cent.	Megaloblasts, per 100 W.B.C.	Normoblasts, per 100 W.B.C.	Reticulocyte, per cent.	Howell-Jolly bodies.
1/4	20	0.95	1.0	275,000	20,000	57	..	..	36	7	..	..	Few	Moder.	...	Marked		...	Few	Few		
1/6	36	2.44	0.8	....	81,000	37	..	5	58													
1/8	38	1.70	1.1																			
1/11	55	4.31	0.6	....	9,100	22	10	2	46	16	..	..	..	...	...	10	2					
1/12	..	4.00	..	250,000	11,200	14	..	1	72	13	..	..	..	No	...	Mod.	...	10	No	No	5	
1/15	70	...	..	....	11,200	32	..	..	58	10	..	..	..	Moder.	Mod.	Marked		Mod.				

from his urine, and his recovery from the anemia was progressive. Three weeks later he developed an attack of acute tonsillitis, without recurrence of the anemia. He was discharged after four weeks, his physical examination showing a normal child with a normal blood picture.

CASE III.—A. T., male aged six months. The previous history was negative except for facial eczema from one to four months. He was breast-fed for four and a half months, now is on a formula.

Six days before admission to the service of Dr. B. Kramer, the child's appetite became poor. At the same time a persistent and increasing pallor of the skin was noticed. Two days before admission, he vomited some of his feedings, and since the onset has been irritable when disturbed, and apathetic when undisturbed. Physical examination shows a well-developed and well-nourished male child, with marked pallor of the skin and mucous membranes. There is an icteric tint to the skin and scleræ. He does not look acutely ill, but shows muscular hypotonia. The tonsils are moderately enlarged but not congested. The spleen is palpable one finger's breadth below the costal margin. The temperature on admission was 97.6°. The details of the blood pictures are shown in Table IV and chart. The additional associated laboratory findings were: bleeding time, 1.5 minutes; coagulation time, 2.5 minutes; platelets, 275,000. Gastric extraction shows a free hydrochloric acid content of 10 and a total acidity of 55. Fragility test-hemolysis began at 0.42 and was complete at 0.26 per cent salt solution. The Wassermann reaction was negative. Qualitative examination for urobilin in the urine was positive. Here, again, were the evidences of a profound, rapidly progressive anemia and accompanying active bone-marrow response. A transfusion of 150 cc. of unmodified blood was given on the day of admission, with an immediate improvement in the blood picture. In forty-eight hours the hemoglobin rose from 20 to 36 per cent, the red cells from 950,000 to 2,440,000. The subsequent improvement was slow, and a second transfusion of 150 cc. was done on the fifth day, following which, the hemoglobin rose to 55 per cent and the erythrocytes to 4,310,000 within seventy-two hours. Two months after discharge from the hospital, the child presented a normal blood picture, and physically the child was normal except that the spleen was just palpable at the costal margin.

Summary of Three Cases Previously Reported and Three Cases Now Presented. All 6 cases presented similar clinical and hematologic pictures, with certain variations. The age incidence was from six months to thirty-five years. Five were in males and 1 in a female. The history of onset in 3 cases was three days, in 2 cases, six days and in 1 case, two days. The onset in all 6 was characterized by the rapid development of pallor, icterus, weakness and rise of temperature. In 4 there was vomiting, diarrhea in 1, backache in 1, headache in 1 and hemoglobinuria in 2. On physical examination, 6 showed pallor and icterus, and 5 fever, while in 4 there was noted splenic enlargement and in 3 hepatic enlargement. The classical evidences of hemolysis were demonstrable in all. The peculiar blood picture described in the previous communication was common to all cases. In general, a very profound anemia, rapidly progressive, marked leukocytosis (a modified leukemoid picture: Krumbhaar[8]) and an erythroblastemia dominated the blood picture. The presence of megaloblasts, especially, is to be emphasized.

Careful and persistent questioning failed to elicit any history pointing to an agent that might explain the hemolysis. In one case it was thought the child might have swallowed a small amount of camphor, and in another there was a questionable history of sore throat. In neither could the facts in the histories be substantiated. Case I was complicated by manifestations of renal insufficiency. Although he became comatose, and chemical examination of the blood revealed nitrogen retention, his urine never contained leukocytes or casts. Apparently the condition was rather one of mechanical retention due to obstruction of the excretory apparatus of the kidney by the detritus from the enormous erythrocyte destruction. This is substantiated by the observations that the urine which he voided during the early part of his illness was thick and syrupy red, evidence of glucose retention and oliguria. This condition resembles, according to Wolbach[9] a fatal form of hemoglobinuria occurring in horses known as azotemia.

The prompt cessation of the hemolysis after transfusion was just as striking as in the 3 previous cases, as was the rapid rise in the hemoglobin percentage and red cells. Reëxamination of all 6 cases, months after recovery showed no sequelæ or recurrences. Physically they are normal and blood examination reveal no abnormalities.

In view of Christiansen's observation of a recovery in his case without transfusion and the experience of the writer with two cases in adults, namely, cases B. L. and L. B. described in 1925, it appears that the cases may be divided into two groups. In one, the clinical course is rapid, the anemia developing with great speed and presenting an alarming clinical picture. This occurs especially in the infants. The other group is a group which runs a slower course and, as Christiansen puts it, is perhaps of a more benign character. The writer fully agrees with Christiansen that transfusion may not be necessary in all cases, but considering the precarious hematologic and clinical states of some of the patients studied, transfusion was considered an imperative procedure. In comparing the length of convalescence of Christiansen's case to the milder cases treated by transfusions there seems to be no question that transfusion hastens recovery to a marked degree.

All attempts to determine the excitant of the disease have been unsuccessful. In none has any history been elicited pointing to any of the usual or unusual causes of hemolytic anemias. The physical conditions of the patients on admission precluded any attempt to make any prolonged cultural investigation before instituting therapy in the form of transfusion, which has constantly terminated the process. Aërobic blood cultures have been uniformly sterile.

Conclusions. Three cases of an acute hemolytic anemia are described in addition to the 3 cases reported in 1925, and references to 2 others in the literature are included.

Eight cases in the literature conform clinically and hematologically to those described previously, 6 recovering permanently after transfusion of unmodified blood, 1 after transfusion with citrated blood (Holst[6]) and 1 without transfusion.

In two of the recent cases hemoglobinuria was present.

One case was complicated by uremia, due apparently to mechanical interference with renal function.

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ERYTHROBLASTEMIA OF INFANTS (VON JAKSCH'S DISEASE).

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In 1889 and 1890 Rudolf von Jaksch[1] described an anemia of infants, characterized by deficiency in hemoglobin and in number of erythrocytes, marked anisocytosis and poikilocytosis, numerous nucleated red cells in the circulating blood, moderate and persistent increase of lymphocytes, and enlargement of the liver and spleen. This author also observed leukocytes containing phagocyted erythrocytes or fragments of erythrocytes. He suggested the name "anemia infantum pseudoleukemica" for this disorder. It is, however, commonly designated as von Jaksch's disease.

Charles Luzet,[2] in 1891, defined infantile pseudoleukemia as a disease peculiar to nursing infants, of unknown etiology, developing insidiously, characterized by severe anemia, enlargement of liver and spleen, large number of nucleated red cells in the blood, some of them in karyokinesis, and a moderate increase of leukocytes. Luzet regards the abundant erythroblasts and the mitotic erythroblasts as the outstanding features.

B. S. Denzer,[3] in 1927, inclines to the view that the term anemia infantum pseudoleukemica of von Jaksch has been applied to various diseases of infants, some of which may well be placed in the accepted groups of secondary anemias and others more properly designated as true leukemias. He does, however, recognize the existence of a small group of infantile anemias which cannot thus be classified. These present anemia, splenomegaly, lymphocytosis and abundant nucleated red cells in the circulating blood.

The infantile hematopoietic system is obviously much more labile than that of the adult, as has been emphasized by Evans and Happ.[4] It is probable that an agent, which would induce only an ordinary secondary anemia in the adult, might, in the infant, cause an anemia with abundant erythroblasts in the circulation. Erythroblasts are the normal blood cells in the earlier months of fetal life. They are commonly seen in the blood of newborn premature infants and are not regarded as abnormal in the newborn at full term. Hence, the peculiarity of the anemia of von Jaksch may depend essentially upon the infantile response. These authors regard rickets and other nutritional disorders of infancy as possible factors in the anemia.

T. B. Cooley[5] has recently suggested that the term von Jaksch disease, be discarded. He regards the disease as an entity, characterized especially by the age of the patient and the large number of erythroblasts in the circulating blood, and prefers the designation, erythroblastic anemia.

During the past eight years, there has occasionally been admitted to the Babies Wards at the New York Post-Graduate Hospital an infant showing a blood picture such as that described by von Jaksch.

Case Reports. CASE I.—H. H., male, aged nine months, was born at full term, weighing 9 pounds at birth. Three older children in the family were well and the history of the parents was negative. The patient had been pale and jaundiced since birth. He was breast fed for three months and since then received modified cow's milk. He had no visible teeth and had never been able to sit up or to creep. Upon admission, the infant was pale and malformed, with a square head, prominent parietal bosses, short nose, malformed external ears, eyes of Mongolian appearance, protruding tongue, neck short and thick. Rachitic costochondral beading was evident. Liver and spleen were very large, the latter occupying nearly the left half of the abdomen. There was a slight umbilical hernia. The blood Wassermann test was negative. A diagnosis of Mongolian idiocy was made.

TABLE I.—BLOOD PICTURE OF CASE I.

	June 23	June 27	July 5	July 9
Red cells	2,344,000	..	3,080,000	2,368,000
White cells	19,800	14,600	16,100	14,100
Hemoglobin (in grams per 100 cc.)	6.1	..	8.3	7.3
Differential Count (per cent).				
Polynuclears	33	30	50	40
Small lymphocytes	4	15	3	46
Large lymphocytes	38	35	47	14
Mononuclears	11	3		
Transitionals	2	3		
Eosinophils	..	2		
Basophils	3	1		
Myelocytes	9	1		
Disintegrated cells	..	10		
Nucleated Red Cells per 100 Whites.				
Normoblasts	10	65	42	25
Microblasts	1	17		
Macroblasts	8	40		
Megaloblasts	3	3	1	

Blood examination on June 23 showed a marked deficiency in hemoglobin and erythrocytes (Table I). The nucleated cells observed in the leukocyte count numbered 24,000 per c.mm., but among these were numerous nucleated red blood cells, 10 normoblasts, 8 macroblasts and 3 megaloblasts being observed in a count of 100 leukocytes. By correcting for these, the total count of white blood cells becomes 19,800. In the stained film, the red cells showed considerable anisocytosis and poikilocytosis. One polychromatophilic megaloblast in mitosis was seen. The lymphocytes and mononuclear leukocytes, together, made up 53 per cent of the white blood cells or 10,500 per c.mm. of blood. The opinion, therefore, tended toward a diagnosis of lymphatic leukemia, possibly initiated by some underlying septic condition.

On June 27, blood examination showed 32,800 nucleated cells per c.mm. of blood. More than half of these were erythroblasts, 125 nucleated red cells to 100 leukocytes in the stained film. The corrected leukocyte count was, therefore, 14,600 per c.mm., of which 53 per cent were lymphocytes and mononuclear leukocytes. The abundant nucleated red cells in the stained film showed very little polychromasia. In nearly all of them, the cytoplasm stained* a salmon pink color, so that they could be easily distinguished from the lymphocytes, in which the faintly reticulated cytoplasm was stained blue.

The patient was given iron citrate by hypodermic injection, beginning on June 28, and $\frac{1}{4}$ grain of thyroid extract with the six-o'clock feeding. On July 2, Fowler's solution was given, 1 minim twice a day and later three times a day. On July 2, the patient was discharged with very little improvement. On July 18 he was brought to the Clinic. Orange juice was added to the feedings and the previous medication continued. It has since been learned that shortly after this last visit to the Clinic the patient died, but no autopsy was obtained.

Case II.—S. M., male, aged five and a half months, was admitted August 28, 1922. The family history was negative. The patient was born at term, weighing 12 pounds. He had been exclusively breast fed. Since the age of six weeks he had appeared pale, according to the mother, and the skin had shown a progressively increasing yellow tint. Vomiting had been frequent. Upon admission to the hospital, the infant appeared fairly well developed and well nourished, without gross evidence of deformity. The skin was pale lemon color, the conjunctivæ, lips and buccal mucous membrane pale. The thorax appeared normal and without signs of rickets. The abdomen was distended and in it the enlarged spleen was very evident, extending below the iliac crest. The lower edge of the liver could be felt three finger breadths below the costal margin. The cervical, axillary and inguinal lymph nodes were enlarged.

Blood examination on August 28 showed only 3 gm. hemoglobin per 100 cc. of blood and red cells 2,084,000 per c.mm. The leukocytes numbered 50,000 per c.mm. (corrected count) and of these the lymphocytes and mononuclear leukocytes made up 73 per cent, or 36,500. In the differential count of 100 leukocytes, 92 nucleated red cells were seen (see Table II). On September 2, a transfusion of 120 cc. was given and on September 27 a second transfusion amounting to 140 cc. of blood. On the next day, September 28, the red cells were 4,179,000 per c.mm. and erythroblasts were not found in the stained film. The child was also given citrate of iron and Fowler's solution. On October 24, he was discharged, generally improved. On this day his blood examination showed 3,916,000 red cells, 9.2 gm. hemoglobin per 100 cc. and 9600 leukocytes per c.mm., of which 73 per cent were lymphocytes and mononuclear leukocytes. In the count of 100 leukocytes, 3 nucleated red cells, all normoblasts, were seen. On November 23 the patient died, the cause of death being given as anemia infantum.

* The tetrachrome blood stain was used.

TABLE II.—BLOOD PICTURE OF CASE II.

	Aug. 28	Sept. 2	Sept. 7	Sept. 27	Sept. 28	Oct. 10	Oct. 16	Oct. 24
Red cells	2,084,000	Trans-	3,632,000	Trans-	4,179,000	3,808,000	3,184,000	3,916,000
White cells	50,000	fusion	18,800	fusion	27,000	10,200	13,200	9,600
Hemoglobin (gm. per 100 cc.)	3.0	with	7.6	with	8.9	9.6	7.0	9.2
Differential count (per cent)		120 cc. blood		140 cc. blood				
Polynuclears	22		24		18	18	34	20
Small lymphocytes	44		54		62	63	34	48
Large lymphocytes	28		19		20	14	22	19
Mononuclears	1		3		..	5	5	6
Transitionals	1		..		..	..	5	5
Eosinophils	4		..		..	..	..	2
Basophils	..		..		..	..	..	..
Myeloblasts	..		..		..	..	..	..
Disintegrated cells	..		..		..	..	..	..
Nucleated red cells (per 100 whites)								
Normoblasts	36		19		..	..	..	3
Microblasts	49		14		..	..	..	..
Macroblasts	7		1		..	..	..	..
Megaloblasts	..		..		..	..	..	..

CASE III.—N. I., aged six months, was admitted to the hospital on December 1, 1922. The family history was negative. The baby had been born at term with easy normal labor. He was breast fed for three months. On account of vomiting and loss of weight, he was then brought to the Clinic. Supplementary feeding with Dryco milk powder was given. Nearly three months later he was again brought to the Clinic, on account of fever and coughing. At this time an examination of the blood (on November 29) showed 1,808,000 red cells per c.mm., 3.9 gm. hemoglobin per 100 cc. and 23,000 white cells per c.mm. The patient was admitted to the hospital on December 1. At that time he was described as a dusky, anemic, undernourished and underdeveloped infant of six months, with open anterior fontanelle but without cranial deformity. There were no teeth. Lymph nodes were not palpable. Slight costochondral beading was recognized. Moist râles were heard at the base of either lung. The abdomen was distended, without rigidity or tenderness. The enlarged spleen extended nearly to the median line and almost to the pelvic brim. The liver extended 2 inches below the costal margin.

On December 4, an examination of the blood showed 1,648,000 red cells per c.mm. and 2.9 gm. hemoglobin per 100 cc. The count of nucleated cells was 23,400 per c.mm. The differential count showed 61 nucleated red cells (28 normoblasts, 25 microblasts, 7 macroblasts and 1 megaloblast) to 100 leukocytes. The corrected leukocyte count, therefore, became 14,500 of which 46 per cent were lymphocytes. The red cells showed marked poikilocytosis and anisocytosis and slight polychromatophilia and granular degeneration. Two macroblasts and one megaloblast were found in mitosis. A transfusion of 180 cc. was given on December 7, and on December 8 the red cells numbered 4,224,000 per c.mm. and the hemoglobin amounted to 10.4 gm. per 100 cc. The nucleated cells numbered 35,400 per c.mm. The differential count showed 110 nucleated red cells (69 normoblasts, 26 microblasts and 15 macroblasts) to 100 leukocytes. Hence the corrected numerical count of the leukocytes became 16,850. $\frac{100}{210} \times 35{,}400 = 16{,}850$. Ten days later the leukocytes had decreased to 8200 per c.mm. and nucleated red cells were not to be found.

In January the patient developed a purulent otitis media, first on the right side and then on the left. The anemia grew more severe, so that on

March 9 the red cells had fallen to 846,000 per c.mm. and the hemoglobin to 1.8 gm. per 100 cc. A transfusion of 200 cc. on March 12 was followed by an immediate improvement in the blood and a gradual healing of the ear condition. On April 6 a foul mucous shred was returned from each ear at irrigation and subsequently the irrigating fluid came away clear. On April 27 the patient was discharged, generally improved. The patient was afterward brought to the Clinic for four successive visits from May 14 to May 28, showing some improvement in appetite and in general symptoms, but after the last visit, his condition grew worse and about fifteen days later he died.

TABLE III.—BLOOD PICTURE OF CASE III.

	Nov. 29	Dec. 4	Dec. 7	Dec. 8	Dec. 18	Jan. 2	Feb. 5	Feb. 12	Mar. 9	Mar. 12	Mar. 13	Apr. 9
Red cells (millions per c.mm.)	1.8	1.6	Trans-	14.2	4.4	4.1	2.1	2.4	0.8	Trans-	4	3.7
White cells (thousands per c.mm.)	23	14.5	fusion	6.8	8.2	11	11.4	7.4	10.6	fusion	6.2	7
Hemoglobin (gm. per 100 cc.)	3.9	2.9	180 cc.	10.4	9.1	7.6	5.8	5.8	1.8	200 cc.	11.5	7.1
Differential count (per cent)			of blood.							of blood		
Polynuclears	39	48		42	40	55	54	30	54		60	45
Small lymphocytes	57	29		35	36	2	23	24	13		17	27
Large lymphocytes	3	17		14	20	15	11	23	10		8	16
Mononuclears	..	1		1	1	14	7	14	3		6	7
Transitionals	..	3		4	2	8	1	4	3		2	5
Eosinophils	1	1		1	..	5	3	3	1		4	..
Basophils	..	1		3	1	1	1	2	..		3	..
Myeloblasts	..	..		..	..	..	..	..	3		..	..
Disintegrated cells	..	..		..	..	..	..	..	13		..	..
Nucleated red cells (per 100 whites)												
Normoblasts	..	28		69	..	1	1	..	2		5	..
Microblasts	..	25		26	..	..	1	1	1		5	..
Macroblasts	..	7		15	..	1	..	..	2		2	..
Megaloblasts	..	1		..	..	..	..	..	..		..	..

Discussion. These three patients are examples of a rather peculiar anemia of young children, the most striking feature of which is the unusually large number of nucleated red cells in the circulating blood, at times outnumbering the leukocytes. The blood picture thus resembles von Jaksch's disease, though the uniformly relatively rapid fatal outcome, differing from the majority of such cases, suggests that they may represent a more definite subgroup. In addition, there is usually an evident enlargement of the spleen, sometimes of the liver also, and a marked relative and absolute increase of the lymphocytes in the circulating blood. The features of the disorder appear to be sufficiently distinct and definite to justify its recognition as a disease entity.

The etiology is obscure. There appears not to be a familial factor, nor is there any suggestion of tuberculosis or syphilis in the etiology. The children in this series were born at full term, which would appear to exclude prematurity as a factor. There is possibly a suggestion that a disordered digestive function may be the underlying cause of this sort of anemia and the marked increase of lymphocytes in the circulating blood might be regarded as a result of gastrointestinal irritation. Recent research[6, 7] upon intestinal bacteria in relation to anemia suggests that studies of intestinal bacteriology might help to elucidate this disease.

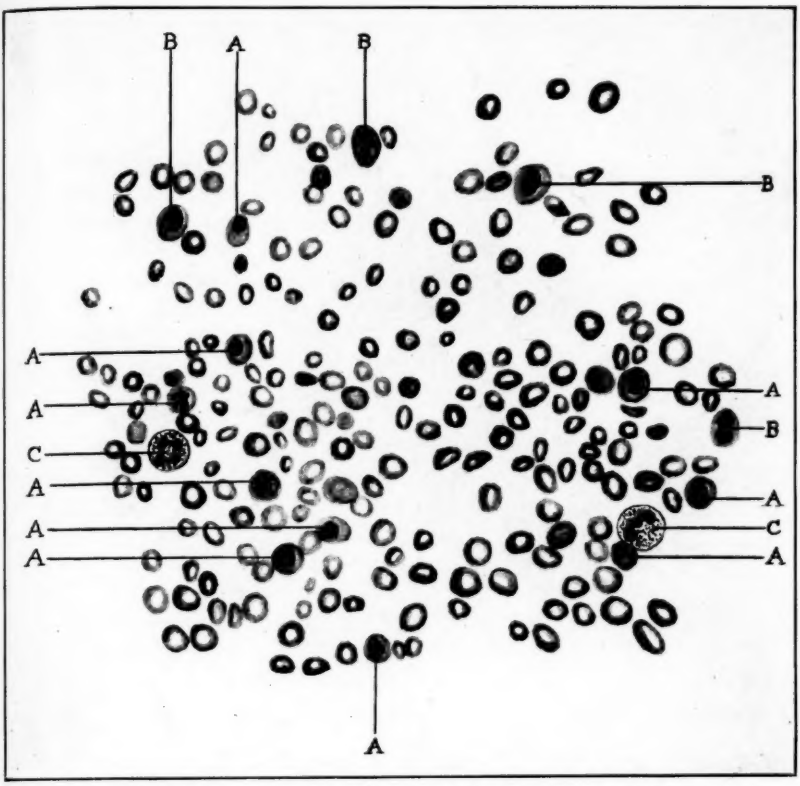

FIG. 1.—Portion of smear for differential count taken from Case I on June 27. *A*, normoblasts; *B*, macroblasts; *C*, polymorphonuclear neutrophil leukocytes.

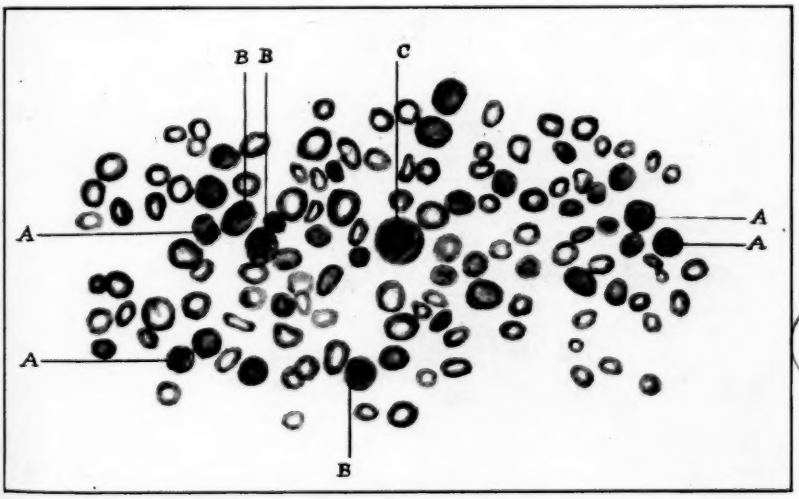

FIG. 2.—Another field from the same smear. *A*, normoblasts; *B*, macroblasts; *C*, megaloblast.

On the basis of the clinical features and the anatomic changes in the blood, even without an understanding of the etiology, it seems wise still to regard this disorder as a disease entity. The suggestion of Cooley that it be designated as erythroblastic anemia or erythroblastemia appears excellent, as it places emphasis upon the most strikingly peculiar anatomic feature of the disorder. However, the name of von Jaksch will doubtless continue to be employed in the designation of this and other anemias in children with a similar blood picture for some time to come.

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PAIN OF CENTRAL ORIGIN.

A Discussion of Some Diseases of the Central Nervous System in which Pain is a Main Symptom*

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All progress in our understanding and knowledge of the human body has been from the periphery to the interior; parts readily reached in exploration yield many of their secrets long before the deeper lying structures. It was known for untold ages that irritation of a sensory nerve was productive of pain. Later it was discovered that the dorsal nerve roots possessed the same function, but only in recent years has it been appreciated that the deeper-lying spinal cord and brain (that is, central nervous system) will respond by

* Submitted for publication, May 3, 1929.

painful sensations to noxious stimuli. In the same sense, it has long been understood that diseases of the peripheral nerves and their roots usually are painful whereas morbid processes centered in the brain and cord are not often attended with suffering. Although the latter statement is true in a general way, there are enough instances of pain central in origin to make the phenomenon by no means a rarity.

Many workers have contributed their share in demonstrating the existence of pain of central origin as well as of the diseases with which it is associated, and there are many theories concerning the mechanism involved in its production. The literature on the subject is already voluminous and it is beyond the scope of this article to enter into all the theoretic considerations of the causation of the phenomenon and its relation to the functions of sensation as a whole. The attempt here will be to discuss the more common clinical conditions associated with pain of central origin and corresponding with different levels of the central nervous system. It may be mentioned that pains not associated with obvious organic lesions, the various types of so-called psychalgia or pains of hysterical, neurasthenic and altogether psychoneurotic origin, have considerable interest in themselves but do not lend themselves to the elucidation of a problem such as this. Only instances were studied wherein the pain was produced by a definite structural alteration of the central nervous system, whatever the cause.

In order to start with simpler structures and to pass to those more complex, the levels of origin of central pain are followed up the pathways of incoming sensory impulses, through the spinal cord and brain stem, into the cerebrum, and finally to their destination in the cortex.

Lesions of the Spinal Cord. Among the many different lesions involving the spinal cord, it is difficult to understand why so seldom pain is produced that may be considered of central origin and quite apart from that due to involvement of the dorsal roots. In an article regarding traumatic lesions, Holmes described a group of patients who, during the World War, received gunshot injuries affecting the spinal cord indirectly. The majority of these patients had wounds in the neck near the cervical portion of the spinal cord and which usually affected one side of it by concussion, so that a Brown-Séquard syndrome resulted. Almost immediately following the injury there appeared below the level of the lesion burning, shooting, stabbing pain that was more marked in the lower extremity that had become paralyzed but that remained normally sensitive. This was poorly described and poorly localized by the patient. It was increased by peripheral stimuli, particularly by passive movement of the leg or even by jarring of the bed, and it was seldom severe or persistent in the side that was anesthetic to pain, touch or temperature. Pin prick and thermal stimuli were extremely

unpleasant and resulting responses tended to radiate widely over the limb, although the thresholds for pain and thermal stimuli were unaltered or even slightly raised. The pain reached its maximum in about two or three days and then gradually disappeared in about three weeks. Holmes considered the pain in the limbs to be due to a lesion of the cord that, although injuring and irritating the fibers carrying impulses of pain, did not destroy them. Possibly the spinothalamic tracts were concerned in this pain but since vibration stimuli produced painful and unpleasant sensations, Holmes considered that the dorsal columns were at least partly responsible. Foerster has observed similar cases and mentioned one case in which, following injury to the cord, an imperfect Brown-Séquard syndrome resulted. Right-sided spastic paralysis of the leg and left-sided thermanesthesia were present, but disturbance in perception of pain was not observed; the patient complained of a persistent severe pain in the left leg. In more severe direct lesions to the cord, hematomyelia may result and at the time of its formation, especially in the cervical part of the cord, this may produce pain in the lower extremities.

Syringomyelia in the majority of cases runs a completely painless course to its end; the painlessness of burns, cuts and bruises in anesthetic areas is a classical feature of the disease. Yet cases of syringomyelia have been reported wherein pain was persistent throughout the course of the disease. Oppenheim remarked that pain is not uncommon, and Raymond and L'hermitte described a spinal form of syringomyelia characterized by intense pain. Schlesinger, Haenel, Dejerine and Thomas, and Taylor, Greenfield and Martin also described cases wherein pain was a prominent symptom. Harris, in a recent article, mentioned that pains in the back and limbs may sometimes precede for years any sensory or motor symptoms in this condition and stated: "The possibility of such aching, boring, burning neuralgias being due to this form of chronic spinal disease is perhaps hardly sufficiently insisted on."

Earlier authors ascribed the origin of the pain in syringomyelia to involvement of the dorsal roots by associated meningitis. Later it was admitted that it might occur from irritation of the intramedullary pain tracts and thereby produce pain remote from the site of the lesion or that it might even be segmental in distribution and due to the syringomyelic cleft involving the dorsal horns of gray matter in the cord. Spiller[25] recently supported the latter hypothesis by the publication of the case of a patient he had examined, including details learned at necropsy. The patient had complained of spontaneous, dull, aching pains in both lower extremities. Examination of the cord, however, showed that the syringomyelic cleft had not reached the lumbar region and that the roots supplying the lower extremities with their meninges were entirely normal. It was, therefore, a reasonable conclusion that the pain was due to

involvement of the spinothalamic tracts above the segmental area supplying the lower extremities. In such cases of syringomyelia the distribution of pain may be bilateral, as in the case of Spiller, or down one complete side of the body. More frequently, however, the pain is segmentally distributed as in the following illustrative case.

Case Reports. CASE I.—An unmarried woman, aged twenty-two years, came to the Mayo Clinic, June 15, 1926, complaining of pain in the neck and back. She never had been very robust, and at the age of eleven years severe, sharp pain developed over the left side of the neck, extending down the posterior aspect of the arm and settling in the left wrist. She had had these attacks of pain over a period of six or seven months when they had gradually diminished, leaving occasional dull, aching pains throughout the posterior aspect of both arms and extending to the wrists. Since this first attack of pain, the left hand had been somewhat weaker, deeper red and perspired more easily. Four years before sharp, shooting pains had developed which had radiated from the right side of the neck and mastoid region up toward the vertex. These pains had been associated with a feeling of stiffness in the muscles of the neck, and they disturbed her sleep at night. Attacks of these pains would last from two to four days, with relief for another few days and then would appear again. About the same time as the pain in the neck and head had appeared she had begun to suffer from a similar type of pain in the left lumbar region. This would radiate from about the region of the third lumbar vertebra, laterally around the trunk toward the anterior-superior spine of the ilium. This pain had been of the same sharp, shooting character, and during one period had been present daily for five weeks. The patient had thought that heat would relieve the pain in her back and, accordingly, she had used a hot-water bottle frequently on that area. At the same time she had noticed that the sensation of heat was not very well felt in the painful areas, and on one occasion at least she had fallen asleep on a hot-water bottle and had burned herself severely without being conscious that she was doing so. The periods of pain had become more and more frequent until, when she came to the clinic, they were usually constant, dull and aching in type, with exacerbations of sharp, shooting pain, especially on exposure to exertion and excitement.

On general examination, the most conspicuous feature on inspection was the peculiar appearance of the left hand. This was soft, atonic, red, flabby, sweating and atrophic, and there was a much greater number of creases on the palm than on that of the other hand. There was definite weakness of the muscles of the hand; the atrophy was mainly in the interossei, opponens pollicis and hypothenar muscles. The grip was weak and the tendon reflexes were absent on the affected side. Also, on the right side, the biceps reflex was lost, but the triceps and supinator reflexes were still active. Hoffmann's sign was present on this side. The patellar and Achilles' reflexes were exaggerated. The plantar reflexes were flexor in type, and the abdominal reflexes were absent on the right side. Horizontal nystagmus when the patient looked to the right, and unsustained vertical nystagmus were present. Over the back, about the region of the eighth to the twelfth thoracic segments on the left side, there was the scar of a healed burn. There was marked diminution of sensation, especially for pain and temperature, in a capelike distribution over the neck and shoulders, in or about the region of the second, third, fourth and fifth cervical segments; tactile sensibility was normal. In the region of the lumbar pain, that is, in the segments supplied by the eighth to the twelfth dorsal

roots on the left side, there was an area of hyperesthesia to temperature and pain which included the area of the burn (Fig. 1). In neither of the areas mentioned was there complete anesthesia for painful stimuli, but a marked diminution in ability to feel pin pricks. Moderate scoliosis in the dorsolumbar spine was observed.

A diagnosis of syringomyelia was made and treatment with Roentgen rays was given over the cervical and thoracic portions of the spine. The patient was requested to return for further treatment, but did not do so. When last heard of, February 15, 1929, she was apparently still suffering, but information could not be obtained as to the exact status.

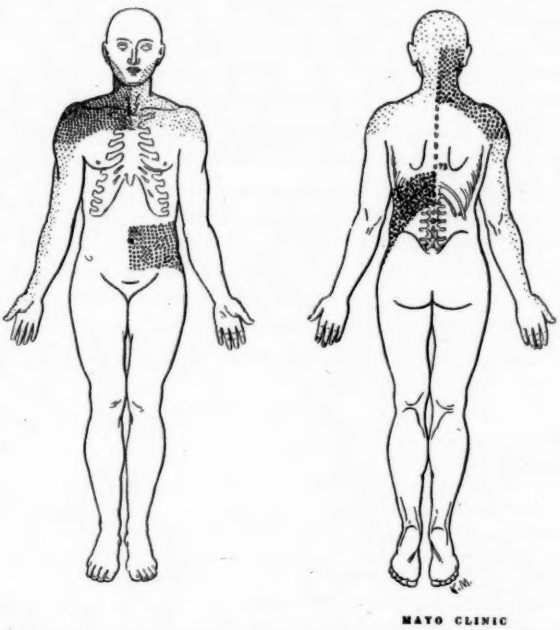

FIG. 1.—Sensory chart in the case of a patient with syringomyelia accompanied by severe pain. The stippled areas represent diminution to pain and thermal sensibility. Anesthesia was not complete.

Similarly to syringomyelia, it is possible for hydromyelia to cause pains by compression of the spinothalamic tracts and posterior columns of gray matter in the cord. Foerster reported the case of a patient whom he had operated upon for intramedullary tumor. There were pains in the fifth thoracic segmental area, paralysis of the legs, incontinence of urine and hypesthesia for all kinds of sensation from the sixth thoracic to the third sacral segments. The patient also complained of severe pain in both lower extremities. At operation a hydromyelic cyst was found at the sixth thoracic segment. It was opened and there was prompt relief of all pain. The paralysis improved also but gradually it returned.

Both intramedullary and extramedullary tumors which involve

the spinal cord sometimes produce pains that are not segmentally distributed and due to compression of the roots but that are situated in regions well below the site of the lesions. Considering how frequently the spinothalamic tracts are involved by compression in cases of tumor, it is surprising that this does not occur more frequently. Elsberg mentioned having a number of cases in his series of tumors of the spinal cord wherein the first symptom complained of was pain in a part of the body distant from the region supplied by the nerve roots at the level of the tumor. This is relatively more common in tumors of the cervical and upper thoracic regions. Often the pain is felt in a lower extremity, on the side opposite to that of the tumor; it may come on early in the course of the compression of the cord by the tumor and before root pains appear. Also, root pains may never appear and these distant pains may constitute a prominent symptom. These manifestations are very confusing and might suggest that the tumor was situated low in the lumbar or sacral part of the spinal canal, when, as is later demonstrated, the pain was due to irritation of the spinothalamic tracts high in the cervical region and on the opposite side. Also, it is not uncommon to find patients, who have had tumors of the spinal cord removed, suffering from constant, severe, burning pains in the lower extremities; the pains appear coincident with the lessening of the anesthesia and during convalescence from operation. Later, with the restitution of both motor and sensory function, these pains disappear.

Case II.—A woman, aged fifty-one years, was brought to the Mayo Clinic, November 3, 1926, because of paralysis of the lower extremities. Eleven months previously she had noticed twitching and quivering of the muscles of the calves of the legs; this condition persisted intermittently throughout the winter. Six months before admission she had noticed that on walking her limbs were not clearing the floor and that there was a tendency to hit against obstacles in her path; this was somewhat worse on the right side. This weakness, clumsiness and stiffness of the lower extremities had persisted, gradually getting worse, and finally reaching the stage of complete paralysis two months before admission to the Clinic. Five months before, and for a period of two or three months, she had suffered intense pains in both lower extremities, chiefly in the posterior aspect of the limb. The pain had extended as high as the hips. This pain had been felt deep in the leg, had disturbed her sleep at night and had not responded to any of the ordinary methods of treatment. Gradually, however, with the onset of numbness and loss of sensation of both lower extremities, this pain had disappeared. The numbness had increased and reached a level about the region of the umbilicus. Incontinence of urine had appeared about twelve days before examination.

Examination disclosed complete paralysis of both lower extremities, of the muscles of the lower part of the back and of the abdominal muscles. There was anesthesia for pain, tactile and thermal sensibility as high as the ninth thoracic segment on the left and the tenth thoracic segment on the right. Tendon reflexes were exaggerated in the lower extremities, and Babinski's sign was present bilaterally. A positive Queckenstedt test was revealed after spinal puncture.

The patient was operated upon, November 11, 1926 (Adson), and a subdural, extramedullary meningioma was found opposite the sixth and seventh thoracic vertebræ, on the right dorsolateral aspect of the cord. The tumor was oval, about 15 mm. long and 12 mm. in diameter. The cord was compressed to about two-thirds of its normal size.

After a somewhat prolonged convalescence the patient made a good recovery.

Experimentally pain may be produced by irritation of the structures within the spinal cord. Dusser de Barenne injected strychnin into the posterior horns in animals and produced severe pain in the corresponding segmental cutaneous zones. By pricking, by cutting and even by touching the anterolateral funiculi, Foerster has produced pain on the opposite side of the body. Once, while injecting a dorsal root with procain, his needle penetrated the dura and stabbed the cord, producing terrific pain in the opposite lower extremity.

Lesions of the Medulla Oblongata. The spinothalamic tracts are continued up into the medulla and, lying dorsolateral to the inferior olivary nucleus, they come in close relationship with the spinal root of the fifth nerve and its nucleus. A single lesion in this region may involve both these structures and may produce anesthesia for pain and temperature on the side of the lesion in the area supplied by the fifth nerve as well as in the opposite side of the body. One good example of such a lesion is the area of softening produced by thrombosis of the posterior inferior cerebellar artery. The whole clinical syndrome produced by this lesion is sufficiently well known not to need further description beyond mention of this crossed anesthesia for pain and temperature that is so characteristic. One of the best reviews written in the past was by Spiller, and more recently Bergmark again has told all that is known about it. It is not generally known that pain may occur in one or more of the anesthetic areas. Among cases described with necropsy, in Wallenberg's case pain was present first in the eye, and later in the entire side of the face on the side of the lesion; this also was present in one of the two cases described by Thomas. In the case reported by Hun, at one time in the course of the disease the patient had pain in the face on the affected side. Among the clinical cases described, Hall mentioned that he had seen a patient who had suffered from occlusion of the posterior inferior cerebellar artery and who complained of considerable pain, which was more or less paroxysmal, on the affected side. In Gowler and Hope's case there was intense burning, tingling, persistent pain over the whole left side of the body and on both sides of the face. Case III presents a similar situation.

Case III.—A man, aged fifty-two years, came to the Mayo Clinic, May 19, 1923, because of pain in the left side of the face and unsteadiness in gait. Seven months before, following a period of great activity in his business, he had a sudden attack of vertigo while at lunch. This vertigo had persisted, and within a few minutes vomiting of a forceful and persistent type

had come on, had continued for several hours and, finally, had been relieved by opiates. The patient had wakened the next morning to find that he had complete paralysis of the muscles of swallowing and his voice was very hoarse. The dysphagia had improved somewhat within forty-eight hours, but thereafter hiccough had come on which had been very distressing and which had lasted four days. The examining physician had noticed at this time some diminution of sensibility to pain over the neck, limbs and trunk on the right side and over the face on the left side. The patient himself had noticed that he had burned the fingers of the right hand with a cigarette and did not feel the burn; there also had been a painless traumatic ulcer in the left nostril as the result of his picking it with his finger nail. After five days in bed, during which time improvement was continuous, the patient had left his bed and had found that he was very unsteady on his feet, with a tendency to stagger to the left; he also had noticed that he had incoördination in the motions of his left arm on attempting to dress himself. The dysphagia had continued to a lesser degree and the hoarseness likwise had persisted.

Three months after the onset, pain gradually had appeared in the face, chiefly in the left temporal fossa, but later spreading over the major portion of the region supplied by the fifth nerve. At first this pain had been intermittent and mild; later it had become constant and intensely severe, representing one of the most prominent features of the trouble. The patient had had considerable difficulty at night from choking and gagging, due no doubt to the pharyngeal paralysis, and, frequently, he would waken coughing and spluttering, at which time the pain in his face would become very intense. Up to the time of examination at the Clinic the pain had been so severe that the patient had needed a considerable quantity of opiates for relief. External stimuli seemed not to have any influence on the severity of the pain. It came and went, irrespective of whatever be might be doing. It was most severe in the left temporal fossa and around the left orbit. An adequate description of its character could not be given by the patient.

On examination, the patient was seen to be a haggard, round-shouldered man, with a somewhat large head, and apparently in very acute pain. Nevertheless his expression was dull and drowsy and his attention was obviously impaired, possibly due to opiates administered for relief of pain. During examination he complained of constant discomfort or pain in the left side of the face; on this pain were superimposed, about every ten minutes, severe paroxysms which made him contort the left side of the face and produced flushing and lacrimation. Horizontal nystagmus and vertical nystagmus, which was well sustained, were present. The left side of the pharynx was paralyzed, as was the vocal cord on that side. There was complete anesthesia to painful and thermal stimuli, as far as could be judged, over the area of distribution of the left fifth cranial nerve, with abolition of the corneal reflex on that side. There was similar but less marked loss of response to painful and thermal stimuli over the right side of the trunk and neck, and in the right arm and leg. Minor degrees of sensibility could not be estimated because of the patient's mental state. Tactile sensibility was everywhere apparently normal, but vibration sensibility was diminished in the limbs on the left side of the body. There was a slight degree of incoördination in the left arm and leg and the gait was moderately ataxic, with a tendency to lurch to the left. Observation of this case was, of necessity, somewhat limited and occupied only a few days. The patient left the Clinic and was not seen again. A letter from his wife stated that, although the pain had somewhat diminished, he died suddenly three months after his departure. The cause of death, as given by the local physician, was a stroke of apoplexy. It was reasonable to assume from our previous study of the patient that he had had another thrombus in the same system of bloodvessels, but extending this time more widely.

It is not only in cases of syringomyelia of the spinal cord that pain may appear but also in cases wherein the same disease attacks the medulla. In the case recorded by Foix, Thevenard and Nicolesco, the patient had at the outset continuous burning pain in the right side of the neck. Later it spread to the face and head. There were also crises of agonizing pain lasting five to ten minutes, mainly spontaneous but frequently initiated by touching or washing the face, stroking the beard, and by currents of cold air. Later the same pain and anesthesia appeared in the opposite side of the face but to a much less degree. Treatment by injections of alcohol into the nerve were of no avail and finally the patient died of an intercurrent affection. At necropsy a syringomyelic cleft was found involving the spinal roots and nucleus of the fifth nerve on the right. It extended from the upper part of this nucleus down to the fifth or sixth cervical segment of the cord and occupied mainly the nucleus of the fifth cranial nerve and the corresponding substantia gelatinosa of the cord. On the left side, in the nucleus of the fifth nerve there was the beginning of gliosis without cavitation.

Foerster had a similar experience with a patient who had a severe trigeminal neuralgic pain at the onset of syringobulbia and before diagnosis was possible. He, however, went further for the relief of this pain and after trying alcoholic injection of the Gasserian ganglion, cut the posterior root of the fifth nerve, without any effect whatever on the pain. Typical signs of syringobulbia ultimately developed and progressed caudad. Pain in the pharynx, ear, occiput and neck appeared in the order given; the pains first appeared in areas of normal sensibility but gradually, as sensation for pain disappeared, the pain diminished.

The visceral afferent component of the vagus, according to Ranson terminates in the nucleus of the tractus solitarius. Its situation just under the floor of the fourth ventricle renders it subject to irritation by tumors occupying this cavity. Nevertheless, although an early and fairly constant symptom of these tumors is vomiting, due in all probability to irritation of the dorsal nucleus of the vagus and its visceral efferent fibers, subjective sensations indicating disturbance of the visceral afferent component are rare. However, Sachs reported the case of a man suffering from a papilloma of the choroid plexus of the fourth ventricle, in whom, as well as the usual vomiting, there was complaint of abdominal pain. At operation, the patient, who had had a local anesthetic, suffered this same pain during the manipulations of the tumor prior to its successful removal. Symptoms of pain also ceased thereafter. I have observed two similar cases of patients with tumors involving the fourth ventricle and wherein the early vomiting so characteristic of the lesion was associated with abdominal pain, poorly localized and poorly described by the patient. Since vomiting and abdominal pain may occur long before increased intracranial pressure has been disclosed

by papilledema and headaches, the vomiting and abdominal pain may be attributed to a condition other than an intracranial disorder, and the result may be a diagnostic error. In the two cases mentioned, examination at necropsy did not show other cause of abdominal pain.

Lesions of the Pons. Just as in the medulla, various lesions situated in the pons may give rise to pain by involvement of the fifth cranial nerve and the ascending spinothalamic tracts. At least two cases of tuberculoma of the pons are recorded with central pain. Economo's patient had pain severe enough to require opiates for relief. The pain was felt in the right side of the body, in the arm, leg, chest and abdomen. Pain was not present in areas supplied either by the left or right fifth cranial nerves. Among other numerous signs of pontine involvement there was also crossed anesthesia for pain and thermal sensibility affecting the left side of the face and the whole right side of the body. Sensibility to touch was everywhere intact. The lesion proved to be a tuberculoma, chiefly on the left side of the pons, and its greatest width was at the region of the main sensory nucleus of the fifth cranial nerve so that both motor and sensory portions of the fifth cranial nerve were severely affected.

The patient of Weisenburg and Stack also had a tuberculoma of the pons and it likewise was unilateral but occupied the right side. It reached its maximal size in the lower part of the pons. Six months after onset of signs of the disease the patient complained of pain in the entire left side of the body, at first intermittent, and later constant. The pain was described as "burning, grinding, disagreeable and unbearable." Later, pain appeared in the right side of the face and there was hyperesthesia to pin pricks in that area. Sensitivity to heat and cold were only slightly diminished on the right side of the face but tactile sensation was almost lost. On the left side of the body, thermal and tactile sensibility were greatly diminished and these stimuli produced marked paresthesia and exaggerated affective reactions.

Herpes involving the fifth cranial nerve, especially in its first and second divisions, is often associated with persistent, severe, constant, burning pain, unpleasant paresthesia and hypersensitivity in the region involved. Particularly in elderly persons, these symptoms may persist for many years after the acute phase has passed. Often the scars which are left are anesthetic or anesthesia may be spread over wider areas and at any time in the course of this so-called postherpetic neuralgia around the forehead, orbit and cheek there may be a strange medley of pain, hyperesthesia and anesthesia.

Injection of alcohol into the nerve or its ganglion, avulsion of the supraorbital nerve and even section of the posterior root of the Gasserian ganglion or avulsion of the ganglion has been done for relief of pain without, however, any constant success. The follow-

ing example represents one in which avulsion of the ganglion failed to relieve the patient's complaint.

CASE IV.—A man, aged fifty-six years, came to The Mayo Clinic, July 14, 1921, complaining of pain in the left orbit and left temporal region. Ten months before, while sitting in the open air, he had noticed some pain and soreness in the left eye. Immediately the eye had become red and swollen and within twenty-four hours this redness and swelling had extended over the left side of the forehead, temporal region and cheek. Accompanying this there had been agonizing pain in the forehead and orbit and for many days he had been delirious with pain and had been under opiates constantly. When pain had somewhat subsided and he was able to observe his condition, he had noticed ulcers over the forehad, cheek and temporal region, and the eye was badly injured. He also had noticed that along with the severe pain there was a certain degree of numbness over the areas of ulceration. Seven months from the time of onset of the illness the left eye had to be removed, and the original pain, although not so intensely severe, had still persisted and was very distressing. At the time of examination, he complained of constant burning numbness in the orbit, temple, forehead and anterior portion of the scalp on the left side.

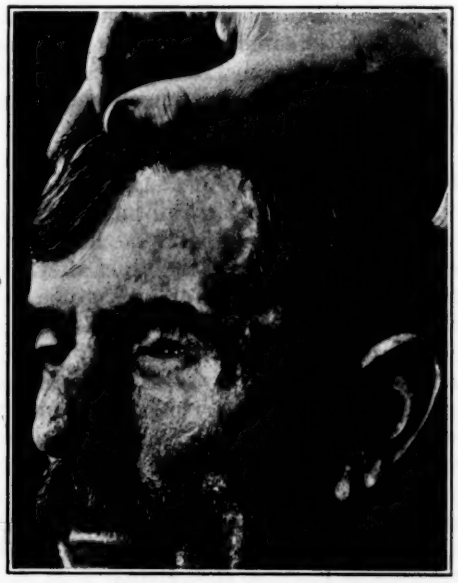

FIG. 2.—Herpes of the left fifth cranial nerve; extensive areas of scarring and loss of the eye are shown.

On examination, the patient was seen to be worn and emaciated, with obvious scarring left by previous herpes of the first and second divisions of the fifth cranial nerve (Fig. 2). The eye socket contained a stump left by previous operation and there was some purulent discharge from the socket. He had rather marked anesthesia for pain, and tactile and thermal sensibility over the forehead, orbit, temple and upper part of the left side of the bridge of the nose. Around the area of deeper anesthesia, over the

scalp, cheek and ala of the nose, were minor sensory changes. The anesthesia largely corresponded in degree and distribution to the extent of scarring. Hyperthesia was not present. The patient was somewhat senile in appearance and reactions, and a moderate degree of peripheral arteriosclerosis was present.

Operation was performed, July 23, 1921. The posterior root was completely cut and the ganglion was avulsed. Convalescence was satisfactory.

On reëxamination, about two weeks after the operation, the patient had complete anesthesia for all qualities of sensation in the area supplied by the left fifth cranial nerve, as well as paralysis of the muscles of mastication. He complained, however, that the pain was still present and, if anything, worse than before the operation. He stated that he felt the pain after operation, as before, in the region of the left temporal muscle, and that it was most severe deep in the socket of the left eye. There also was some pain over the vertex and jaw, where the areas supplied by the fifth cranial and the cervical nerves join. He has not been heard from since.

The persistence of pain in this case may have been due to a lesion in the trigeminal nucleus occurring at the time of the original herpetic attack and therefore refractory to section of the fifth nerve outside the pons. In herpes zoster, the lesions in severe cases are not confined to the spinal ganglions but invade the dorsal horns of gray matter in the cord; the same is probably true in the homologous Gasserian ganglion. Accordingly, residual effects of the inflammatory lesions of the pons and of the tissue around the sensory nuclei of the fifth cranial nerve may serve to perpetuate the patient's suffering.

Lesions of the Optic Thalamus. Although the plan followed so far has been to trace the possible sites of painful lesions up the cord and brain stem to the thalamus, historically at least this organ holds first rank as a source of central pain and other affective phenomena. For a considerable period it has been thought to be the only source. Spiller, in 1922, stated: "I should like to have evidence that a lesion entirely below the optic thalamus may cause spontaneous pain in one-half of the body." It was his privilege in 1923 to fill in this gap in knowledge, ably supported by Weisenburg and Stack. Recent writers, including Wilson, have agreed that spontaneous pains and various types of unpleasant sensations hitherto considered characteristic of lesions of the thalamus may arise as sequels to structural disease anywhere below the thalamic level. Although the so-called syndrome of the thalamus is no longer considered peculiar to thalamic lesions, yet the original work of Dejerine and Roussy is worth recalling; however their interpretation and that of Head may be doubted, it does not dim the luster of their original masterly description.

In 1906, following the observation of a series of 5 patients with focal thrombotic softening in the region of the thalamus, Dejerine and Roussy published a description of what they called the syndrome of the optic thalamus. They defined it as: (1) slight hemiplegia, usually without contracture, and disappearing rapidly; (2)

persistent hemianesthesia, organic in type, and always associated with marked and persistent loss of deep sensibility; (3) mild hemiataxia and astereognosis, the latter more or less complete; (4) sharp, persistent, paroxysmal pains felt in the hemiplegic side of the body, often intolerable and not yielding to treatment, and (5) choreoathetotic movements in the limbs of the paralyzed side. They considered the first three as major features and the last two as being relatively less constant.

The onset of symptoms was sudden but with as little general shock as one would suppose with a small focus of thrombotic softening. Although the motor weakness rapidly diminished, the sensory signs persisted until death, which might not ensue for years. More in detail the sensory disturbance, objectively, consisted of diminution but never of loss of pain, temperature and tactile sensibility, while sensibility to vibration, muscle sense, the power of estimating the weight, size, shape and contour of objects were profoundly affected. Either at the onset of the disease or comparatively early, subjective discomfort appeared not only in the paralyzed limbs but also in the side of the face and trunk. Chiefly, these discomforts were in the form of pains that radiated along the whole length of the limbs affected; they were poorly localized and occasionally were described as being in the skin and subcutaneous tissues. They were constant, with, however, paroxysmal exacerbations severe enough to make the patient cry out and to impair sleep. Not only were the pains apparently spontaneous but they could be evoked by touching the skin, by pin pricks and by cold water. Deep pressure especially was intensely disagreeable. The patients described the pain in many ways and used adjectives such as burning, darting, squeezing and stabbing. Between the crises of pain there was complaint of formication and various types of paresthesia including a sensation of swelling in the limbs, trunk and face.

In the cases studied at necropsy the anatomic lesion found by Dejerine and Roussy was a small focus of softening, chiefly in the lateral nucleus of the thalamus, in its posterolateral part, although the median and internal nuclei and part of the internal capsule were affected to a lesser degree.

Since Dejerine and Roussy's work, contributions too numerous to mention have been published dealing with lesions of the thalamus. Among them is that of Holmes and Head, published in 1911. Later, this work was further elaborated from a study of 24 cases and described in great detail in Head's book, published in 1920. The description given by one of his patients, of her own pains, is worth quoting: "ever since this 'stroke' she has suffered from pains in the left half of the body, and an uncomfortable sensation as if something were crawling under her skin. These pains are intense in the hip, the loin and under the left shoulder. They are said 'to pump up and down the side' and the left arm and leg 'feel as if they

were bursting.' Whenever there was cause for visceral discomfort, such as the passage of a constipated motion, these pains became particularly severe, and the heart is said to 'throb' and the stomach to 'work' painfully, but on the left side only."

In Head's work emphasis is laid on the excessive response to affective stimuli. In all of his 24 cases the response to pin pricks, to extreme ranges of heat and cold and to pressure was intense. The threshold for the stimulus might actually be raised, but once the sensation reached consciousness it was responded to more profoundly than on the normal side. A patient might call a pin prick a touch when lightly applied but if the pressure were increased it finally would produce an intolerable sensation of discomfort. Not only were painful stimuli in Head's cases responded to with this overloading of feeling tone, but agreeable sensations, such as pleasant degrees of heat, were equally intensely felt and responded to with greater pleasure than that felt on the normal side. In these cases also, when a pin was dragged across the body from the normal to the affected side, an intense degree of discomfort was experienced once the median line was crossed.

An interesting feature of thalamic lesions was illustrated also by Head in the effect of emotion on these patients. Music was peculiarly likely to evoke a different reaction on the two halves of the body. One of the patients could not go to church because he "could not stand the hymns on his affected side." In another, during the funeral service for the late King Edward VII, as soon as the choir began to sing he felt "a horrid feeling come on in the affected side and the leg was screwed up and started to shake." In many of these patients, therefore, the mental emotions evoked by music or by disagreeable sounds intensified preëxisting pains and discomfort. Other lesions of the thalamus producing the so-called thalamic syndrome have been described, among which may be mentioned inflammations such as epidemic encephalitis, traumatic lesions and tumors.

CASE V.—A man, aged sixty years, came to the Mayo Clinic, August 13, 1928. He complained of residual weakness of the right side of the body and severe continuous pain over the whole left side. Five years before, while working as a fireman, he had come in contact with a current of 2300 volts and had been severely shocked. He immediately had become unconscious and had remained so for five hours. On regaining consciousness, it has been discovered that he had paralysis of the right side with aphasia and complete anesthesia on that side. He had very little memory as to what had occurred for the first three or four weeks of his illness, but at the end of that time movement had commenced to return on the right side and ultimately had returned to almost normal as far as motor function was concerned. The aphasia had disappeared also within a few weeks, but the right-sided anesthesia, although improved to a certain extent, had persisted and had remained more or less profound up to the time of examination. Pain had made its appearance within a few weeks from the time of the injury, about the time the motor and sensory functions were improving and had reached a marked degree of intensity which had been little lessened

in the five years that had elapsed. He had noticed that the pain was intensified by all sorts of stimuli, such as contact of his clothing with the affected side. Especially deep pressure evoked unpleasant pains and a sensation as if a thousand needles were radiating throughout the limb that was squeezed. For that reason, he avoided shaking hands as far as possible.

Examination revealed a man very well preserved for his age. The tendon reflexes on the right side were hyperactive, but there was good motor function on that side and no sign whatsoever of aphasia. Appreciation of joint movement, vibration and the estimation of weights was almost abolished on the right side. The patient retained some degree of tactile, pain and thermal sensibility. However, the threshold to stimuli was definitely increased. Interpretation of results of tests was difficult because of the markedly effective reaction to all stimuli. A pin prick of the arm, for example, might not be felt at first, but on stronger stimulation was felt as an intense burning pain that radiated up the whole arm into the face. Thermal sensibility was poorly felt until the testing apparatus was made extremely hot or cold; then, the pain was described as being very disagreeable. Tactile sense was the most affected and the lighter degrees of touch were not appreciated at all. Localization of the point of stimulus was practically lost. The patient stated that the only improvement that had occurred in recent years was in the motor functions.

Lesions of the Cerebral Cortex. There has been some difference of opinion on the question of pains arising from cortical lesions. Holmes and Head, for example, have insisted that there is little if any, representation of pain in the cortex and that the thalamus is the essential organ for the reception of impulses carrying affective tone. Corresponding to this, they believe that sensibility to pain is the least altered of all sensibility by destructive cortical lesions. On the other hand, among numerous other observers, including Minkowski, Piéron, Foerster, and Wilson, it is admitted that sensibility to pain has at least some representation in the cortex. Accordingly, they believe the cortical destructive lesions may materially influence the sensibility for pain and that irritative lesions may produce unpleasant sensations, if not actually painful, at least intensely disagreeable. One phase of the problem was investigated by Cushing twenty years ago, with negative results as far as pain is concerned. He stimulated with faradic current the cortex of the postcentral gyrus in two patients who had full consciousness. In one, a sensation described as numbness and, in the other, a tactile impression was felt in the hand of the opposite side. Pain was not complained of by either patient. On the other hand, Foerster, with the same method of electrical stimulation of the postcentral gyrus and superior parietal lobule, claims definitely to have produced painful and disagreeable sensations in various parts of the body on the opposite side. He further stated that pathologic lesions of the cortex can and do produce painful sensations. Clinically, however, it is not often that pathologic irritative lesions produce any marked degree of pain and seldom is it continuous as in that produced by lesions in the thalamus and in levels below it. More often the pains so produced are paroxysmal and appear as a sensory component preceding a Jacksonian or general convulsion. Sensory auras in the

form of tingling sensations, a sensation of formication, wavelike sensations, feelings of constriction, and, according to Foerster, deep, dull pains, may appear in a limb or in one side of the body before convulsive movements begin. It is also common knowledge that painful auras in the form of abdominal pains, especially in children, frequently usher in general convulsive seizures or attacks of petit mal. Foerster mentioned the case of a patient who had pains in the bladder and rectum as an aura preceding Jacksonian attacks. Pains rarely appear in lesions of the subcortical white matter, although cases of this have been reported by Weisenburg and by Mills. In the following case, a tumor involved the cortex and subcortical white matter, apparently sparing the optic thalamus. Although an exact anatomic relationship cannot be determined in infiltrating tumors, it is worth reporting because of the severe pain that accompanied its course.

Case VI.—A woman, aged forty-three years, was brought to the Mayo Clinic, October 11, 1921, because of pain and weakness in the right arm and leg and the right side of the face. Fourteen months previously, while apparently well, she suddenly had been taken with jerking of the muscles of the right arm, face and jaw, in the order mentioned, and she had suffered loss of speech. This lasted only a few minutes but similar attacks had recurred intermittently for nearly two days, and her speech had been very badly affected for that time. There had not been residual weakness, and within a few days after attacks had ceased her speech had cleared up. About the time of the onset of these jerkings she had noticed a burning, aching, full sensation over the right side of the face, which had been constant ever since. Two or three months later the attacks had been repeated and had been followed this time by clumsiness of the right arm, so that she had dropped objects from the hand and had had difficulty in writing. The unpleasant sensation on the side of the face now had passed into the right arm and she had complained of it feeling hot and swollen. Five months from the period of onset, because of the pain and clumsiness in the right arm, a cervical rib had been removed by a surgeon elsewhere. Several weeks afterward she had had, for the first time, general convulsions and had suffered from headaches which had been present chiefly in the morning and had been felt above and behind the left ear. Prior to the attacks of jerking, which never had been very severe, she had experienced a feeling of terror and as if she were going to be hurried away somewhere without her volition. A year from the onset of the trouble the clumsiness in the arm had progressed to the state of definite weakness, and this rapidly had increased, spreading to involve the right leg a few weeks before admission to the Clinic. The pain previously experienced in the arm and face had spread to the leg and she had noticed diminished sensation in the whole region. She was not sure as to when this sensory disturbance first had appeared, but a few months before she had burned her arm severely on the stove without any very marked pain. The headaches had been getting quite severe, mentally she had become more dull, and her speech had become definitely impaired during the last few weeks.

On examination, the patient had obvious aphasia, which, however, was mild in degree and more in the character of hesitation and stumbling than complete loss of speech. Hemiparesis was present on the right side, more marked in the face and arm and to a less degree in the leg. She was still able to walk around but dragged the leg while doing so. There was a moderate degree of diminution of pain, and thermal and tactile

FIG. 3.—Horizontal section of the brain showing tumor involving the cortex and subcortical white matter; the thalamus is apparently intact.

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FIG. 4.—The inferior surface of a horizontal section of the left hemisphere of the brain just above the corpus callosum. The tumor was at its greatest diameter here and involved the cortex in front of and behind the central sulcus.

sensibility over the whole right side without any exaggerated responses. This was not dissociated and seemed to be more severe in the extremities of the limbs, from the elbow and knee down. Joint and vibration sensibility were lost in the upper and lower extremities and complete astereognosis was present in the right hand. The corneal reflex was diminished on the right side. During examination the patient was very emotional, cried frequently, and seemed to be greatly disturbed because of difficulty in speaking. On that account also it was difficult to test her sensations adequately. She had numerous attacks of jerking similar to that with which the trouble had begun. They were not Jacksonian in character, but consisted of intermittent twitchings of the whole right upper extremity, without any order of march. She complained bitterly of constant swollen, hot, full, aching sensations in the whole right side of the body. A diagnosis of tumor in the left sensorimotor cortex was made.

Subtemporal decompression was done, November 14, 1921. The cortex had changed in color and appearance in the region of the central sulcus and it was cystic and fluctuating to touch. The patient died the following day.

At necropsy a soft, degenerating, infiltrating, cystic tumor was found. It was about 6.4 cm. in its greatest depth, and it involved the motor and sensory parts of the cortex as well as the subcortical white substance. Anteroposteriorly it was 5.6 cm. long and involved areas in front of and behind the central sulcus about equally. Above, it reached nearly to the superior margin of the hemisphere, but it did not extend below the lateral fissure or involve the temporal lobe to any marked degree. Medially and above, it reached the level of the lateral wall of the lateral ventricle, but below, it did not extend very deeply and it seemed to spare the thalamus. Microscopic examination of sections taken from the motor and the sensory cortex showed dense infiltration by tumor cells which in places reached the pia mater. Some of the cortical layers were completely destroyed. Sections taken from different portions of the thalamus did not show signs of tumor. The histologic diagnosis of the tumor was spongioblastoma multiforme (Figs. 3 and 4).

Summary and Conclusions. Some of the conditions involving the central nervous system that are productive of pain have been discussed. An attempt has been made to confine discussion to those wherein only the brain and spinal cord have been affected. Lesions of the sensory roots of the spinal and cranial nerves and all peripheral nerves are not discussed. The suffering induced in most of the cases described had been intense, and diagnosis in a few was extremely difficult in the early stages of the disease. The central site of the disease process represents a serious difficulty in attempts at therapeutic relief and as a whole such conditions are not easy to deal with from the diagnostic standpoint. The theories concerning the explanation of the phenomena of pain are complicated and are not based on a sure foundation. For this side of the question, reference may be made to Head, Foerster and Wilson's views on the subject. Clinically, the problem of pain of central origin is interesting; infrequent as its occurrence may be, it well repays study and observation.

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SEASONAL INCIDENCE AND STUDY OF FACTORS INFLUENCING THE PRODUCTION OF ONE THOUSAND RECURRENCES OF GASTRODUODENAL ULCERS IN EIGHT HUNDRED PATIENTS.*

By Moses Einhorn, M.D.,
NEW YORK.

Being particularly interested in the study of ulcer for a number of years, and with some special opportunities for studying it in all of its phases both in America and abroad, I have been impressed by certain important features that were common to all of these cases—characteristic types of pain and its relation to meals, seasonal relationship, the intermittency of the recurrences and the constitutional characteristics, particularly facial expression of the patients.

In this article I shall discuss the study of ulcers merely in one of its phases, namely, the rôle of factors which influenced the production of recurrent attacks of gastroduodenal ulcers, based on 1000 recurrences in 800 patients. In my observations and investigations I have made every effort to obtain a detailed clinical history, not alone of my old patients who returned with recurrences of their symptoms, but also of patients consulting me for the first time, who were formerly treated by other physicians.

Seasonal Incidence. The data of seasonal incidence given in Chart I represents not only recurrences which were under my observation, but also past recurrences, obtained from the clinical histories of the patients.

In present recurrences the following percentages were obtained: fall, 42 per cent; spring, 35 per cent; winter, 19 per cent; summer, 4 per cent; whereas, the percentages of past recurrences were: fall, 46 per cent; spring, 41 per cent; winter, 6 per cent; summer, 7 per cent.

From the above, we note that the results for the fall and spring are about equal, in past and present recurrences, but that they vary slightly as regards the winter and summer seasons. Present recurrences having been based on a more accurate and detailed study may, therefore, be accepted as more exact.

Monthly Incidence. A careful analysis of the frequency of recurrences per month was also made, and is indicated by the dark curve in Chart II. Commencing with the month of January, we note a slight rise in recurrences to 9 per cent, with a decline to 6 per cent during the month of February. Early in the month of March there is a rise to 12 per cent, with minor fluctuations, which remain more or less constant during the months of April and May. Beginning with the month of June, a decided decline to 1 per cent is observed,

* Read before the Eastern Medical Society, New York City, May 10, 1929.

remaining thus through the months of July and August. At the end of this month the percentage rises, reaching its highest point of 20 per cent by the beginning of the month of September. During the month of November there is a gradual decline to 7 per cent, and thereafter remaining stationary throughout the winter months.

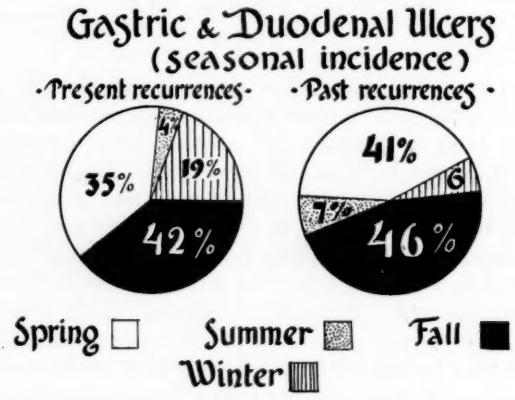

CHART I.

According to the above findings, most of the recurrences occurred during the months of September and May, and a moderate number during the months of March and October. There was a minimum percentage of recurrences in the months of June, July and August.

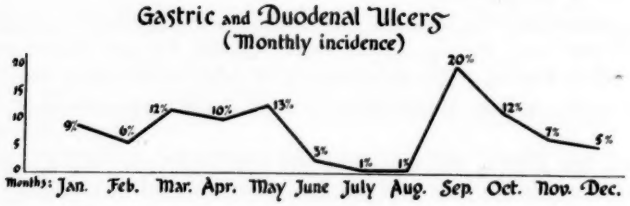

CHART II.

Weekly Incidence. In Chart III two curves are plotted, the light curve representing the months and the heavy curve the weeks. Roman numerals indicate the division of months into weeks. Certain characteristic points in the weekly incidence can be noted from this chart: There is a sudden rise in recurrences from the beginning of the fourth week in February, including the first week in March, which corresponds to the increase in percentage in the monthly incidence. During the fourth week in May until the second week in June there is a decided decline, remaining constant throughout the summer months. Commencing with the third week

in August, there is a gradual rise until the maximum number of recurrences is reached during the second week in September.

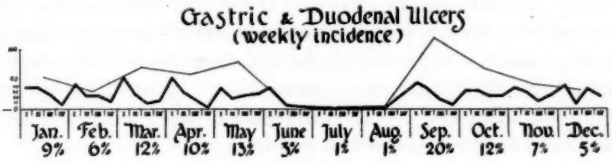

CHART III.

From the above study it is obvious that there are certain definite seasons, namely, the fall and spring, during which the greatest number of recurrent attacks occur. I should like here to advance several reasons which will probably explain this seasonal incidence.

In the summer the ulcer patient leaves the city for a vacation and rest in the country. His life at this time is usually well balanced, his diet regular and he undergoes a minimum of fatigue and exertion during this period. Patients subject to chronic ailments such as pulmonary or cardiac diseases or those susceptible to colds, hay fever or asthma are generally relieved at this time.

With the advent of the fall the patient returns to the city, in order to resume his business activities. In contrast to the rest and relaxation which he enjoyed in the country, he now feels the nervous strain of his new duties and surroundings. These have a marked effect upon the patient who is extremely susceptible to change. His meals become irregular and hurried, and the raw fruits which are now in season do not agree with him. The rainy season too, which now commences, has an effect upon those patients who are subject to chronic diseases and colds.

In the spring the weather changes intermittently from cold to mild, and inasmuch as the patients remove their winter apparel early in the season, before the temperature is yet stable, they are liable to have more colds. Those patients who suffer with hay fever are also greatly annoyed at this time of the year. Then, too, the diet, which is now constituted largely of fresh raw vegetables, seems to have a disadvantageous effect on the ulcer patient.

The Rôle of Factors in the Production of Recurrences. In Chart IV the percentage incidence with reference to colds, psychic load, diet and external pressure is shown.

Colds. Colds are the most important factor, being present in 57 per cent of all recurrences. I was interested also in the degree and intensity of colds, and found in my analysis that the mild cold with the sneezing and running nose constituted the highest percentage; the more severe cold, accompanied by respiratory ailments as bronchitis and sore throat, a moderate percentage and the remaining

small percentage were attributed to the more acute conditions, such as grippe and influenza.

During the months of January and February, 1929, I had the opportunity of studying the effect on the recurrent attacks of gastroduodenal ulcers, of the recent epidemic, which reached the shores of New York and New Jersey about the months of December, 1928, and January, 1929.[1] I was impressed by a number of my old patients, who returned with recurrences, who never before had attacks during this season of the year.

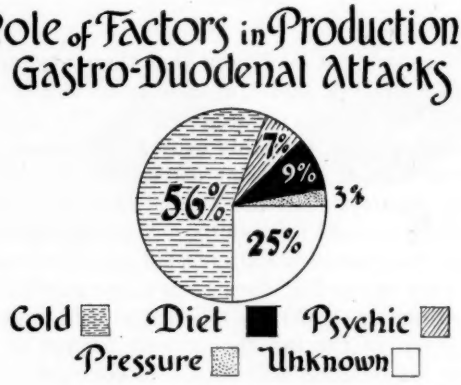

CHART IV.

Upon investigation, I learned that each of these patients, previous to reporting to the office, had been ill with grippe or influenza, the diagnosis having been made by the family physician. I also observed that their gastrointestinal symptoms and the duration of their recovery varied with the severity or mildness of the influenza attack.

Diet. Diet as a cause was found in only 9 per cent of the recurrent attacks, a surprisingly small percentage, in view of the fact that the treatment of ulcer is essentially dietetic.

Psychic Load. Psychic influences, such as anger, shock, emotion and business reverses, play a causative rôle in the development and recurrent attacks of ulcer, the percentage as shown in the above chart being 7 per cent. Several of my cases deserve special mention here, as they represent the type of individual who reacts particularly to emotional disturbances.

One case is that of a broker who reported to my office with a gastroduodenal recurrence induced by sudden fluctuations in the Wall Street market; another patient had a severe attack immediately after suffering heavy losses on the race track; a professional speaker and a musician both had recurrences of symptoms whenever they developed stage fright on appearing before an audience.

Extreme depression caused by the death of a relative, or great happiness, in many cases, brought on an attack. In each instance the onset, which may have been in any form, was necessarily very sudden and not gradual.

External Pressure. External pressure is represented here in only 3 per cent of the gastroduodenal recurrences. A few years ago I made a special study of this factor with regard to the effect of the pressure of belts on ulcer patients.[2] My investigation of this study, which I presented in a separate article, was conducted along the following lines:

A number of patients were selected and divided into two groups: Group I consisted of those who wore suspenders during the period of observation, while Group II was composed of those whom I directed to wear belts. I laid particular stress in this study on ascertaining the difference, if any, as to the time required for the disappearance of the symptoms and also as to the number of recurrences.

On the whole, the symptoms were eliminated more quickly, and there were less recurrences in the suspender group than in the group which wore belts. I was convinced that there is a definite advantage in having the patient wear suspenders instead of a belt.

In spite of the careful and detailed analysis which was made, 25 per cent of the cases still remained in which no definite cause for the recurrence could be ascertained.

Our findings in a study of the seasonal relationship and the probable cause of recurrences in a follow-up of 100 cases of gastroduodenal ulcer[3] were about the same as those given here.

Summary. 1. There are certain definite seasons, namely the spring and fall, during which most of the recurrences of gastroduodenal ulcers occur.

2. The largest number of recurrences occur during the months of September and May, a moderate number during March and October and a minimum percentage during the months of June, July and August.

3. There is a rise in recurrences beginning the fourth week in February, including the first week in March; a decline during the fourth week in May until the second week in June; a gradual rise commencing the third week in August until the second week in September, at which period the maximum number is reached.

4. Colds, diet, psychic load and external pressure are several factors which play an important rôle in the production of recurrences.

5. In 25 per cent of the cases there are no definite factors to which the recurrent attacks of gastroduodenal ulcers can be attributed.

Comment. There are certain critical periods for each individual ulcer patient and recurrent attacks will generally occur at a given time in these patients. It is, therefore, important to ascertain the exact critical period of the patients, in order to prevent these

recurrences. Each patient should be instructed to report for treatment a few weeks prior to the probable period of the recurrence, even though he may be feeling well at that time.

In following this outline of treatment, I have been successful in preventing gastroduodenal recurrences in a number of my patients.[4]

Only when the patient learns to follow the above instructions, can we hope to prevent recurrences and ultimately obtain better results in the treatment of gastroduodenal ulcers.

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AMŒBIC ABSCESS OF THE LIVER: REPORT OF FOUR CASES IN THE NORTH TEMPERATE ZONE.*

By Philip W. Brown, M.D.,

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Abscess of the liver due to Endamœba histolytica in the North Temperate Zone is of sufficient rarity to warrant reporting 4 cases which were observed in 1928 at The Mayo Clinic. During the preceding seven years only 6 other cases of amœbic abscess had been recorded at the Clinic although search for the amœba had been made in other cases in which abscess of the liver had occurred.

The disease has been the cause of serious concern in the tropics and it is by authorities working there that knowledge of this complication of endamebiasis has been advanced. It is largely due to Rogers that the more effective management of amœbic abscess of the liver has been established. In a group of 2516 cases, he found a mortality of 56.7 per cent, but after introduction of the combined treatment by emetin and aspiration, the mortality in 111 cases was 14 per cent. He quoted Chatterjee, who later recorded only 1.6 per cent mortality in 186 cases. The splendid work of Ludlow in Korea should be noted; he had a mortality of 8.8 per cent in 160 cases. Closer study of his report shows that in 43 cases in which aspiration and emetin were employed, the mortality was only 2.3

* Submitted for publication June 4, 1929.

per cent. From northern Africa comes another excellent report by Lacase who had a mortality of 8 (3.1 per cent) in 252 cases. Lacase advises emetin and aspiration but does not hesitate to undertake an open operation in suitable cases.

The abscess may be single or multiple. Lacase noted that the abscesses were multiple in 53 cases, about 20 per cent, of a series of 252 cases of amœbic abscess. Ludlow noted that multiple abscesses were present in 10 per cent of 160 cases. McGlannan quoted Rogers, who holds that there were single abscesses in 51 per cent of a series of cases, two or more large abscesses in 25.8 per cent, and one large abscess together with several small abscesses in 24.4 per cent. Ludlow emphasized alcohol as a possible predisposing factor, for white people of the tropics are more subject to abscess than natives, and especially is this true in alcoholic patients.

An antecedent history of diarrhea usually is obtained, and was elicited in the 4 cases of the group to be reported. Cort reported hepatic involvement in 97 cases of 530, and in this 97, there was a history of diarrhea. Ludlow elicited a history of diarrhea in 137 of 160 cases, but he observed that diarrhea is such a common occurrence in the tropics that an occasional spell of diarrhea may be forgotten.

Report of Cases Observed in The Mayo Clinic. CASE I.—A man, aged twenty-three years, a resident of Indiana, said that for several months he had had an occasional spell of mild diarrhea. Twelve weeks prior to admission to the Clinic pain had appeared in the right lower part of the chest and upper right portion of the abdomen. This had been accompanied by fever and loss of weight.

General examination revealed nothing of moment other than tenderness in the upper right quadrant of the abdomen. There was leukocytosis of 29,000 with 16 per cent lymphocytes; 7.5 per cent large mononuclear leukocytes; 2.5 per cent transitional cells, and 74 per cent neutrophils. One examination of stool gave negative results and the roentgenogram of the chest did not reveal abnormality.

Right pleurocentesis was done and in the aspirated fluid Endamœba histolytica was identified. Treatment by means of 0.65 gm. (10 grains) emetin hydrochlorid hypodermically and 6 gm. of treparsol (formin derivative of meta-amino-para-oxyphenyl-arsenic acid) orally, both in divided doses was instituted. During this treatment aspiration was done several times, as there proved to be a large abscess of the right lobe of the liver which was of such size as to all but preclude possibility of its being absorbed. At the end of thirty-three days' hospitalization the patient was dismissed in excellent condition. Further treatment, in divided courses of auremetin (hydrogen periodid of emetin and auramin) and treparsol was advised.

CASE II.—A man, aged twenty-five years, a resident of Indiana, three months prior to admission had had bloody dysentery which persisted with varying intensity. He had begun to lose strength, and rather abruptly had begun to cough up blood and foul sputum. Six weeks prior to admission resection of a rib in the lower right part of the thorax had been done, with a resulting discharge of bloody pus. On admission, there was still diarrhea, but the most striking feature was the constant cough and raising of dark, bloody, chocolate-colored pus. The patient was so weak and dyspneic

that it was difficult to obtain a history. He seemed to be half drowned in the secretions of the lungs.

General examination revealed in the right lower part of the chest marked dullness which extended almost to the fourth rib anteriorly. A discharging sinus was present in the right side of the chest. The temperature was 103° F. The hemoglobin was estimated at 47 per cent; erythrocytes numbered 3,310,000 and the leukocytes varied from 14,800 to 28,100. Roentgenograms of the chest revealed fluid at the base on the right side.

Because of the pronounced thoracic symptoms, the preliminary impression was that possibly a malignant condition was present. Thoracentesis was done, and growths were not obtained on culture; however, in other cultures, and also by means of smears, Endamœba histolytica was identified. Just prior to this disclosure, Endamœba histolytica was identified in the stools. The usual treatment by emetin and treparsol was instituted. While the patient was under treatment copious, spontaneous drainage developed at the site of the former rib resection and a tube was inserted. The patient's convalescence was gradual at first, but after fifty-three days he was dismissed from the hospital in excellent condition. Further antiamœbic treatment was to be carried out at home.

Case III.—A man, aged thirty-six years, a resident of Wyoming, had contracted dysentery while in Texas eight months before he was seen at the Clinic. A diagnosis of amœbic colitis had been made and 0.77 gm. (12 grains) of emetin had been administered in divided doses. He had suffered a recurrence in about four weeks and had received 0.77 gm. (12 grains) more of emetin and 10.5 gm. of stovarsol both in divided doses. He had remained free of trouble until two weeks prior to admission, when chills and fever had appeared and pain had developed in the lower right part of the chest. His physician, who had had military service in the Philippines, had aspirated the liver and had identified Endamœba histolytica. He then had referred the patient for further treatment.

On admission the patient had fever and the temperature ranged as high as 101.5° F.; hemoglobin was estimated at 65 per cent. Erythrocytes numbered 3,980,000 and leukocytes 11,700, with a differential count of 26.5 per cent lymphocytes; 2.5 per cent large mononuclears; 69.5 per cent neutrophils; 1 per cent eosinophils and 0.5 per cent basophils. Stools contained Endamœba histolytica and Giardia lamblia.

Roentgenographic studies of the chest and colon and a proctoscopic examination, gave negative results.

The patient did not seem acutely ill, so that medical management, without aspiration, was carried out. He received 0.5 gm. (8 grains) of emetin and 6 gm. of treparsol, both in divided doses. At the end of nineteen days of hospitalization, he felt very well and was permitted to leave. He remained well only six or seven weeks, when the diarrhea recurred, and ten days later the pains in the hepatic region returned. On readmission, treatment consisting of 0.2 gm. (3 grains) of emetin, 4 gm. of treparsol, and about 20 gm. of yatren, all in divided doses, was administered. In spite of this he continued to fail. The temperature rose to 103° and leukocytosis of 14,000 cells was present. Through a posterolateral incision, about 1 liter of thick, dark, odorless pus was drained and smears made from the pus revealed Endamœba histolytica. Postoperative convalescence was uneventful except that the parasite persisted in the pus from the draining sinus. Irrigations with solution of quinin then were advised and persistence in taking interrupted courses of emetin and treparsol was urged. At the time of the patient's dismissal his condition was satisfactory, although there was still slight drainage.

CASE IV.—A woman, aged forty-seven years, a resident of Illinois, during the two years previous to admission to the Clinic had had an occasional spell of mild dysentery which had seemed to clear up without any particular medication. For about ten years she had had attacks of right upper abdominal pain associated with fever.

On admission, she complained of pain in the area of the liver and tenderness in this region was elicited. Her temperature was as high as 103°. The hemoglobin was estimated at 42 per cent. Erythrocytes numbered 3,000,000 and leukocytes 14,000 with a differential count of lymphocytes, 9 per cent; large mononuclear leukocytes, 3.5 per cent; transitionals, 2 per cent; neutrophils, 84 per cent; basophils, 0.5 per cent. Two examinations of stools revealed only Endamœba coli. Roentgenographic studies of the chest, colon and stomach gave negative results.

A positive diagnosis was not possible, although there was some reason to think that the patient might be suffering from empyema of the gall bladder or abscess above or below the liver. While she was under observation, in the hope that the acute process would subside and permit a more favorable time for exploration, a course of emetin and treparsol was administered. There ensued an abrupt and spectacular response to treatment, so that, after the completion of a course of 0.65 gm. (10 grains) of emetin and 4.25 gm. of treparsol, both in divided doses, the patient was permitted to return home and there to carry out further antiamœbic treatment.

Comment. This group of 4 cases presents several of the unusual phases of the management of amœbic abscess of the liver, both from the diagnostic as well as from the therapeutic standpoints. Objection might well be made to considering Case IV as an instance of hepatic abscess, especially as a case of abscess due to amœba. There is no positive confirmation of the diagnosis by laboratory methods but one would not expect so spectacular and so abrupt a response to treatment if the symptoms were due to a pyogenic infection of the gall bladder or liver. The indeterminate features of this case and the history of diarrhea fully justified the therapeutic trial. Certainly 0.24 to 0.40 gm. (4 to 6 grains) of emetin hydrochlorid can be given in divided doses with little or no risk and if the symptoms are due to the amœba, there is almost always a decided response. To carry out a prolonged therapeutic trial may prove unwise, but a short course of treatment may prevent many further difficulties. If such a large abscess is present in the liver that it cannot be absorbed, aspiration can be carried out with little or no risk, and from the aspirated fluid, smears and cultures may be made and examined for Endamœba histolytica.

Case I illustrates the effect of aspirating a large abscess, and aspiration was repeated several times in this case. Antiamœbic treatment in such a case is of the utmost necessity; yet it is expecting a great deal to assume that the body can absorb as large an accumulation of pus as was present.

Case III would seem not to conform with the statement of Rogers that abscess develops only in untreated or in insufficiently treated cases. A reasonable amount of antiamœbic treatment had been administered early in the stage of dysentery, before the patient

arrived in Rochester, yet the treatment can be criticized on the ground that follow-up examinations were not made and that the treatment was not varied. Prior to his first admission, therefore, the patient can be considered to have had insufficient treatment. During his first period at the Clinic, his response to treatment was as striking as that of the patient in Case IV. Further treatment was advised. However, symptoms relative both to the bowel and to the liver recurred, and this in spite of treatment that had been so intensive that complications such as neuritis were feared. At this stage, yatren was tried and a small amount of emetin and treparsol was given without benefit. Surgical drainage of the huge abscess demonstrated why medical management no longer would be of help, and yet the development of such an abscess, under intensive treatment, gives cause for anxiety. Such cases must be infrequent, and fortunately so. Suitable drainage followed by careful, interrupted treatment eventually should produce a cure. It is possible that the abscess was present at the first admission and that antiamœbic treatment was sufficient temporarily to halt the process but that the disease had established too firm a hold on the liver to be aborted. Also, aspiration at that time might have obviated the necessity of the patient's returning the second time.

Case II is the most remarkable one of this small group. On first appearance the patient seemed to be not much more than able to keep alive. The constant productive cough and dyspnea which all but precluded speech and prevented his lying down, dominated the picture. There occur many scattered references to rupture of amœbic abscess of the liver through the diaphragm and finally into a bronchus. The case reported here, therefore, is by no means unique. The size of the abscess was such that antiamœbic treatment would not have sufficed. Fortunately, there was a sinus through which adequate drainage established itself; also the patient had been fortunate in not having suffered even more serious difficulties at the time of the resection of the rib. It is conceivable that the resection may have been a factor in the rupturing of the hepatic abscess into the bronchial tubes, although this would probably have occurred, due to the protracted illness of the patient.

Summary and Conclusions. 1. Amœbic abscess of the liver in the North Temperate Zone occurs infrequently.

2. The recognition of Endamœba histolytica as a possible cause of hepatic abscess must not be overlooked. Failure to recognize it may lead to serious complications, and abdominal exploration in such cases is dangerous.

3. Treatment of amœbic colitis must be carefully and thoroughly carried out and extended examinations of stools should be made. This should prevent the development of hepatic abscess except in the occasional case.

4. An antecedent history of diarrhea is not always obtained, although it was elicited in the four cases reported here.

5. Tenderness in the region of the liver, fever, and leukocytosis are the usual features that direct attention to hepatic complications in a case of endamœbiasis.

6. Emetin and treparsol, in conjunction with as conservative an operation as possible, preferably aspiration only, is the method of choice in dealing with amœbic abscess of the liver.

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REVIEWS.

PRACTICAL LOCAL ANESTHESIA. By ROBERT EMMETT FARR, M.D., F.A.C.S. Pp. 611; 268 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1929. Price, $9.00.

THIS, the second edition of the author's work on Practical Local Anesthesia, is a distinct addition to the literature. The so-called melodramatic features, such as photographs of "smiling patients" which seem to be indicated from the educational standpoint in the first volume, have been deleted and their place taken by numerous well-executed drawings following the technique of the Brödel school. The text is valuable alike to the beginner and the experienced operator. If an objection could be offered it would be directed against the including of case reports. A man with the experience of the author does not need such reënforcement to his text. The work is a thoroughly good one. E. E.

LABORATORY METHODS OF THE UNITED STATES ARMY. Edited by CHARLES F. CRAIG, M.A., M.D. Pp. 696; 9 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $3.50.

STARTING as a war manual, this useful little book edited by a well-known authority, now takes its legitimate place in the civilian laboratory. With new sections in this edition on Protozoölogy, Helminthology, Entomology and Veterinary Methods, though small in size, its scope is considerable. Clinical Pathological Methods (218 pages) and General and Special Bacteriological Methods (210 pages) comprise the bulk of the book, but in addition to the new sections mentioned, there are also parts on examination of water, sewage, meat and dairy products, alcohols, also on disinfectants, water sterilization and pathological (really postmortem) methods.

While completeness can hardly be expected in a production of this kind, one misses a number of desirable methods; in the blood section, for instance, I find no reference to such simple useful tests as the erythrocyte fragility, the reticulocyte count and the sedimentation time. While useful up to a certain point, then, such small manuals cannot be expected to give as satisfactory service as the larger books. E. K.

HUMAN HELMINTHOLOGY. By ERNEST CARROLL FAUST, PH.D., Pp. 616; 297 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $8.00.

A WELL documented volume, presenting a wealth of information on the parasitic helminths of man. Introductory remarks include general discussions of the history and modern development of the subject, parasite and host adaptation, factors influencing parasite distribution, and specific names as determined by the International Code of Zoölogical Nomenclature. The taxonomy and biology of the large groups are next considered, followed by detailed accounts of life cycles, diagnosis, therapeusis and prophylaxis of both important and incidental species. Chapters on special laboratory technique and methods of diagnosis, and on the intermediate hosts of the worms are included. The text is well illustrated with original photographs and drawings, certain life cycles being presented graphically. Although much is included that will interest only the specialist, the book will be a valuable aid to the student, the clinician and the pathologist. H. R.

STERILIZATION FOR HUMAN BETTERMENT. By E. S. GOSNEY, B.S., LL.B., and PAUL POPENOE, D.Sc. Pp. 202. New York: The Macmillan Company, 1929. Price $2.00.

CALIFORNIA has conducted an experiment of the utmost importance in application of modern surgery to race betterment. More than six thousand mental defectives have been legally sterilized in that state over a period of twenty years. The surgical, biological and social data of that large scale experiment have been collected, and published in technical journals. The present book represents a summary of the chief findings, written in very readable form indeed. Bibliography and summary of the present legal status of sterilization are appended.

If the intrinsic interest of the California sterilization program were not in itself sufficient, it would become so through a recent decision of the United States Supreme Court sustaining a state sterilization law, and asserting that "three generations of imbeciles are enough." S. M.

THE BLOOD PICTURE. By PROF. DR. VICTOR SCHILLING. Translated and edited by R. B. H. GRADWOHL, M.D. Seventh and Eighth Revised Edition. Pp. 408; 48 illustrations. St. Louis: The C. V. Mosby Company, 1929.

As is to be expected in a book by Schilling, the blood smear, the hemogram and the thick drop are especially emphasized; in fact,

ordinary leukocyte, erythrocyte and hemoglobin determinations are relegated to the "auxiliary method" group. While such strivings toward greater technical simplicity may meet with favor in Germany the trend in this country is definitely toward the elaboration of laboratory diagnostic methods, especially when, as in this case, facts of value are lost in the simplifying process. Emphasis is also placed on tropical methods (from which the book in the original German grew), on vital stains, and on Schilling's new nonspecific "guttadiaphot" test. The presentation of the leukocytic nuclear shift is thorough, well done and extremely valuable, as one would expect from its most active exponent. No one reading this section should remain in doubt as to the value of the method to clinical medicine and surgery. This country has hitherto been slow to appreciate its advantages. E. K.

MODERN METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., with Chapters on Special Subjects by various collaborators. Third edition. Pp. 815; 95 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $10.00.

A BRAVE attempt to include in one volume every department of medical therapeutics. In this edition, the sections on diathermy, liver in anemia, iodin in goiter, and nonspecific protein therapy have been revised and several new drugs added. Even a reasonably complete presentation of such a wide range could not be expected and is not found. The lack is at least partly compensated for by a vigorous, interesting style of presentation which does not hesitate to call a spade a spade. E. K.

THE FEMALE SEX HORMONE. By ROBERT T. FRANK, A.M.,M.D., F.A.C.S., Gynecologist to Mt. Sinai Hospital, New York. Pp. 298; 86 illustrations and 36 graphs. Illinois: Charles C. Thomas, 1929. Price, $5.50.

THIS monograph presents from both a laboratory and clinical standpoint the results of many long and painstaking researches on the internal secretions of the female reproductive organs. The first section of the book deals with the history of the biologic, pharmacologic and chemical investigations, and evaluates and correlates many partly related studies. Here, also, is found the technique for the author's blood test for the female sex hormone.

The second, or clinical, section deals with a study of the blood of five hundred women by this test. The results are classified under various functional and clinical headings, and suggestions are given for the study and treatment of these conditions. Full proof is

furnished for the author's nihilism in regard to present-day therapy by ovarian substances, and other related products, as recommended by biologic manufacturers. It is only to be hoped that a therapeutic agent for hypofunction of the ovaries as reliable as the proposed diagnostic test is simple will soon be forthcoming. There is a copious bibliography attached to each section, and an authors' index. The book closes with a review and summary of the present status of the famale sex hormone. This monograph will undoubtedly be of great interest to all physicians concerned with the endocrinology of the female. P. W.

DE OCULIS. By BENEVENUTUS GRASSUS. Translated by CASEY A. WOOD, M.D., LL.D. Pp. 101; 5 illustrations. California: Stanford University Press, 1929. Price, $5.00.

BENEVENUTUS GRASSUS, also known as Benevenutus De Salern or Hierosolimitans, probably a Jewish physician of the eleventh century wrote a practical treatise on diseases of the eye that was highly esteemed by medieval surgeons, and for five hundred years was the most popular manual on the subject. It also has the distinction of being the first printed book on ophthalmology, the incunabulum having been printed at Ferrara, as the translator of the present book shows in his introduction, in 1474. There are 22 manuscripts and about 18 printed editions of this text, though but very few copies are extant, a list of which are given at the end of this volume. Dr. Casey Wood's translation is welcome addition to medicohistorical literature, especially with its instructive introduction and in the pleasing form that the Stanford University Press has given it.

E. K.

TUBERCULOUS INTOXICATION. By JOSEPH HOLLOS, M.D., Pathologist of St. Vincent's Hospital, Staten Island, New York. Pp. 132. New York: William Wood & Co., 1928. Price, $3.25.

THE author believes that an antitoxic and lytic immunity develops in latent tuberculosis and that hypersensitiveness is brought about by the liberation of endotoxins from the dissolved tubercle bacilli. As a consequence of this hypersensitiveness a condition of tuberculous intoxication results, which manifests itself in disturbances of the endocrine system, neurasthenia, rheumatism, epilepsy, thyrosis and in various other ways.

According to Dr. Hollos the tuberculous intoxication may be cured by the use of Spengler's immune blood, which is prepared by hemolysing the washed red blood cells of immunized rabbits. This treatment has been discredited and no critical evidence is presented in this volume to justify its use. J. A.

A Study of Masturbation and Sexual Life. By John F. W. Meagher, M.D., F.A.C.P. Neurologist to St. Mary's Hospital, Brooklyn; Consulting Psychiatrist to Kings Park State Hospital; and so forth. Second edition. Pp. 130. New York: William Wood & Co., 1929. Price, $2.00.

This author speaks with pride of the favorable reception accorded the first edition and the subject certainly merits scientific consideration, since: "Not only physicians, but clergymen and teachers are often consulted by parents, and by the youths themselves, for advice in regard to disturbances which they attribute to this habit."

N. Y.

An Introduction to Pharmacology and Therapeutics. By G. A. Gunn, M.D., Professor of Pharmacology in the University of Oxford. Pp. 213. New York: Oxford University Press, American Branch, 1929.

This little book is essentially a pocket edition of Cushny's textbook of pharmacology. Brevity is achieved by selection of salient features, which are thoroughly treated, and by omission of controversial points and of the evidence upon which current idea are based. The book provides an admirable birds-eye view of the essential features in the actions of practically all important drugs. It was not intended to replace more comprehensive textbooks, but to provide a background for them. It is heartily recommended to the student, intern, and physician who wishes to reëstablish his conceptions of drug actions.

C. S.

The Conquest of Cancer by Radium and Other Methods. By Daniel Thomas Quigley, M.D., F.A.C.S. Pp. 539; 334 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $6.00.

This book appears to have been written by one intelligent and optimistic, in enthusiastic praise of the virtues of radium in the prevention and cure of malignant tumors.

It contains much that is true and good, and the author and some of his patients are to be congratulated upon the excellent results obtained in many of the reported cases.

But is is clear, from the beginning to the end, that the author's scientific background is somewhat hazy, and his pathology original. In consequence the work is full of categorical statements and dogmatic conclusions that cannot fail to astonish the readers.

To him cancer is not a great unknown disease: he knows all about it. See how he explains it: "The period of development of a

carcinoma in an area where it can be studied through all its various stages, such as a cancer developing on the lower lip, shows that the precancerous disease is a definite injury, a definite poisoning, and a definite infection by extrinsic agents. These agents produce a benign ulcer. During the period of extrinsic influence and the period of benign ulcer, the time element is very much greater than the time element involved in the development of neoplastic tissue, as a parasite, up to the point where pain and bleeding and cachexia lead the victim eventually to die the 'stinking death.'"

See also his final conclusion: "We probably know more about cancer than about any other chronic disease. Instead of being hopeless from the standpoint of cure, *it is probably the most easily and surely curable of any of the chronic diseases.*"

Think of that in the face of the multitudinous controversial questions as to its origin and nature, and especially in view of its ever increasing incidence and appalling death rate! J. McF.

THE ROBERT JONES BIRTHDAY VOLUME. A COLLECTION OF SURGICAL ESSAYS. Pp. 434; illustrated. New York: Oxford University Press, American Branch, 1929. Price, $13.00.

THIS volume of surgical essays has been contributed to by twenty-four of the great writers of the world who were friends or pupils or who had been associated with him during the World War. The essays are all on clinical subjects of extreme importance to surgeons, internists and orthopedists. Many of these essays are classics and when grouped in one volume as this and prefaced by such a master of diction as Sir Berkeley Moynihan, the whole constitutes a collection that should be of great value to its readers.

The book is nicely made, beautifully edited and abundantly and profusely illustrated. E. E.

SOME PRINCIPLES OF MINOR SURGERY. By ZACHARY COPE, M.S., M.D., F.R.C.S. (ENG.) Pp. 159; 82 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.50.

THE writer has undertaken a difficult task in presenting a work of this character because whatever he includes or excludes in the subject matter there will always be some critics who will criticize omission or commission. He wisely does not claim to have written a minor surgery but has confined his efforts to presenting in detail many of the minor principles that are so often omitted from the larger works as being too unimportant to occupy valuable page space.

To students both undergraduate and postgraduate it can be of great help, especially in the trying days of early practice. The reviewer recommends it as such very highly. E. E.

BOOKS RECEIVED.

NEW BOOKS.

*Clinical Obstetrics.** By PAUL T. HARPER, PH.B., M.D., SC.D., F.A.C.S. Pp. 629; 84 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $8.00.

*Hemorrhoids—The Injection Treatment and Pruritus Ani.** By LAWRENCE GOLDBACHER, M.D. Pp. 205; 31 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $3.50.

*The Treatment of Varicose Veins.** By T. HENRY TREVES-BARBER, M.D., B.Sc. Pp. 120; 11 illustrations. New York: William Wood & Co., 1929. Price, $2.25.

The Surgical Clinics of North America (Lahey Clinic Number). Vol. IX, No. 6. December, 1929. Pp. 188; 51 illustrations. Philadelphia: W. B. Saunders Company, 1929.

The Medical Clinics of North America (New York Number). Vol. XIII, No. 3. November, 1929. Pp. 272; 58 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*Coronary Thrombosis: Its Various Clinical Features. (Medicine Monograph XVI.)** By SAMUEL A. LEVINE, M.D. Pp. 178; 85 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, $3.00.

*Blood Grouping in Relation to Legal and Clinical Medicine.** By LAURENCE H. SNYDER, SC.D. Pp. 153; 28 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, $5.00.

Progressive Medicine, Vol. IV, December, 1929. Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 357; 80 illustrations. Philadelphia: Lea & Febiger, 1929.

NEW EDITIONS.

*The Treatment of the Common Disorders of Digestion.** By JOHN L. KANTOR, PH.D., M.D. Pp. 300; 88 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1929. Price, $6.00.

Manual of Midwifery. By HENRY JELLETT, B.A., M.D. (Dub. Univ.), F.R.C.P.I., L.M. and DAVID G. MADILL, B.A., M.B., B.CH., B.A.O. (Dub. Univ.), L.M. Pp. 1281; 570 illustrations. Fourth edition. New York: William Wood & Co., 1929. Price, $10.00.

An authoritative work with emphasis on the methods of the Rotunda Hospital. New sections have been added on anesthesia, pyelitis, nephritic and preëclamptic toxemia.

*An Outline of Endocrinology.** By W. M. CROFTON, B.A., M.D. Pp. 163; 53 illustrations. Second edition. New York: William Wood & Co., 1929. Price, $3.00.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Skin Reactions to Filtrates of Hemolytic Streptococci in Acute and Subacute Nephritis.—During the course of a previous investigation HANSEN-PRUSS, LONGCOPE and O'BRIEN (*J. Clin. Invest.*, 1929, **7**, 543) noted that hemolytic streptococci isolated from the tonsils, adenoids or accessory nasal sinuses of cases of acute and subacute glomerular nephritis produced "toxins" which gave skin reactions comparable to those produced by the "Dick Toxin." They noted also that greatest intensity of the skin reactions occurred in those patients suffering from acute and subacute nephritis associated with infections caused by hemolytic streptococci. A systematic study was made of the incidence and intensity of the skin reactions to the bouillon filtrates of hemolytic streptococci in three groups of cases; first, patients with acute and subacute nephritis; second, normal individuals and third, patients suffering from uncomplicated acute tonsillitis. Eighteen strains of hemolytic streptococci were used. They were grown in beef infusion peptone broth. For skin reactions the filtrates were usually employed in 1 to 100 dilutions. When positive reactions were obtainable the dilutions were increased to 1 to 500, 1 to 1000, 1 to 2000. For each test 0.1 cc. of the dilution was employed. Proper controls were used. The skin reactions were observed at the end of eighteen and twenty-four hours and depending upon the size of the diameter of the reaction, they were labeled +, ++, +++, ++++. The reaction of the skin in normal persons and patients suffering from abnormal conditions were as follows: Sixty individuals were tested, 38 of whom gave positive reactions and 15 gave a ++++ reaction. In other words, the patients gave a strong reaction to a dilution of 1 to 100 and of the individuals who gave positive reactions with this dilution, only 9 per cent gave ++++ result with the 1 to 500 dilution. In this control group, the individuals

having tonsillitis or sinusitis gave the strongest reactions. In the group of 27 patients who had nephritis 81 per cent gave positive reactions and two-thirds of the number gave ++++ reactions. These reactions, incidentally, have persisted in the same patients for many months or years. The increased sensitiveness does not seem to depend upon the existence of a demonstrable infection or upon the carrier state. Of the 22 test subjects who had tonsillitis, 95 per cent gave a ++++ reaction. The authors discuss their findings rather fully and conclude that the positive skin reaction is regarded as an evidence of allergy to the hemolytic streptococcus or the product of its growth. The preponderance of strongly positive reactions in the nephritis group indicates that these patients may be highly allergic to the hemolytic streptococcus. The authors suggest that the development of an acute diffuse glomerular nephritis in patients suffering from a hemolytic streptococcus infection may be referable to the products of the growth of the hemolytic streptococcus acting upon previously sensitized kidney cells.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Pain Sensibility.—CROHN (*Am. J. Surg.*, 1929, **7**, 474) states that it has been observed that the constitutional variation in pain sensitiveness alters the clinical history of gastric cases both functional and organic. Not only are the clinical history and the subjective symptoms modified by the degree to which the patient feels pain, but the very course is altered; favorably in those that possess the natural defensive mechanism of pain sensibility and unfavorably for those who by their constitutional deficiency fail to be conscious of so important a protective phenomenon. The hypersensitive individual comes early for treatment and begs relief. The insensitive person is relatively unconscious of his affliction and appears only when a major complication makes it impossible longer to deny the existence of a morbid process.

Correlations of Internal and External Pancreatic Secretions.—(DETAKATS (*Arch. Surg.*, 1929, **19**, 775) says that the splenic portion of the pancreas was isolated from the rest of the gland in 25 dogs. The division with an electric cautery followed by wrapping omentum around the tail seemed the most satisfactory procedure. Specimens were taken from the isolated tail at intervals of from two days to one year. After a short period of edema a gradual destruction of the acinar elements takes place. There is an increasing amount of connective tissue which finally results in pancreatic cirrhosis. The ducts are first dilated, then show proliferation and infolding of their epithelium. Occasionally buds of epithelium form, resembling an early stage of embryonic development. The islands show edema for the first two weeks. Later there appear large solid cell complexes showing the vascular arrangement and staining properties of islet tissue.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

On the Chemistry, Pharmacology and Clinical Actions of Acedicon.—I. The chemistry of Acedicon, which is a shorter name for Acetyl demethylo-dihydrothebain, is discussed briefly by SCHÖPF (*Deutsch. med. Wchnschr.*, 1929, **55**, 302). The substance is closely related to morphin, being an isomer of acetyl codein.

II. WIELAND and BEHRENS (*ibid.*) present a brief summary of the pharmacologic actions of this new compound. They show that, while it is related to the opium alkaloids in many of its actions, it differs from them in a number of details. It does not produce habituation in dogs in the sense that there is no need for increasing the dose to produce a given effect when administration is continued over a long period of time. There are also no withdrawal symptoms. In point of activity on animals it lies midway between codein and thebain, being less toxic than the former. Its actions are exerted chiefly on the central nervous system. The respiratory center is depressed without any of the codein-like stimulation. There is no direct action on the blood pressure, blood-vessels or the heart, except that the latter is somewhat slowed as a result of the central vagus stimulation. It is markedly analgesic, resembling morphin in this respect.

III. Clinical study by NONNENBRUCH and RISCHAWY (*ibid.*) shows that the average single dose is about 10 mg., although larger single doses may be given for severe pain. The daily dose for oral administration to produce satisfactory analgesia or sleep may be as great as 30 to 50 mg. or more. These same doses administered subcutaneously produce similar analgesia and hypnosis in a shorter time (about fifteen minutes) and in greater intensity than when administered by mouth. No observable harmful effects are produced upon respiration or upon the circulation. The drug greatly diminishes the cough reflexes but, unlike morphin, does not seem to check expectoration. Comparing it with morphin, the authors find that a subcutaneous dose of 10 mg. has about the same analgesic action as the same dose of morphin; about half the hypnotic action and about the same depressant action on the cough reflexes. The constipating action on the intestine is very much less than that of morphin. In comparison with codein, acedicon is about four times as active in suppressing cough and it is incomparably more active in analgesic and hypnotic action. So far as observations go there has been no suggestion of habituation in man and, inasmuch as the drug does not produce morphin-like euphoria, a craving for it does not seem likely.

The Action of Lobelin and of CO_2 on Respiration in Narcosis.—FRANKEN (*Klin. Wchnschr.*, 1929, **8**, 439) reports careful and detailed comparative studies of the respiratory stimulation produced in anesthetized man by intramuscular and intravenous doses of lobelin and by the inhalation of 5 per cent CO_2 mixtures. He finds that the intramuscular use of lobelin in the ordinary dose of 10 mg. is relatively inactive in the presence of anesthesia, either by ether, chloroform, avertin or pernokton, all patients having been previously prepared by the administration of narcophin-scopolamin. In many instances, there is virtually no respiratory stimulation from this dose of lobelin. Intravenous administration of doses ranging from 1.5 up to 6 mg. produce marked increase in respiratory rate and volume, but these effects last only one to five minutes. Doses as small as 3 mg. given intravenously also produce some stimulation of the abdominal vagus. While lobelin rouses the patient rapidly from his narcosis, this cannot properly be ascribed to its respiratory effect since its action is too brief to account for adequate exhalation of the narcotic. The action of CO_2 mixtures is incomparably more intense and more effective than is that of any practical safe dose of lobelin and this combination of CO_2 with oxygen or air is absolutely without danger, which is not true of lobelin.

Injections with Harmin in the Treatment of Metencephalitis.—Following Beringer's reports of the actions of the alkaloid banisterin on the extrapyramidal motor system, RUSTIGE (*Deutsch. Med. Wchnschr.*, 1929, **55**, 613) made clinical observations using the chemically identical alkaloid, harmin. He found no influence upon the circulation other than a variable slight effect upon the heart rate. Dizziness, tinnitus and a sense of drunkenness with occasional nausea appeared about fifteen minutes after injection of the drug and varied widely in intensity in different patients apparently without relation to the size of the dose. There was a prompt and very marked diminution in the muscular rigor which, in some patients, amounted almost to complete disappearance. This effect, however, lasted only from a few minutes to a very few hours. Tremor was sometimes temporarily increased but in most instances was diminished or checked for a short period of time. Voluntary movements were markedly improved both in their completeness and the rapidity with which they were carried out. The improvement in this respect appeared in some ten or twenty minutes but had disappeared in all cases within an hour after the dose. In all respects these results were similar to those obtained with banisterin. From the foregoing well controlled observations Rustige concludes that neither harmin nor banisterin is of any important therapeutic value and that neither one offers any prospect of becoming so unless some means be obtained by which their actions can be sufficiently prolonged to make them of clinical value.

Clinical Investigations on the Localization of Action of the Analgesics.—Pointing out that our knowledge as to the precise portions of the brain upon which the local analgesics exert their action is fragmentary, HOFF and WERNER (*Klin. Wochnschr.*, 1929, **8**, 488) report a series of careful investigations carried out in man. Their subjects included normal patients and patients proved to have organic lesions of the optic thala-

mus. As a criterion of the analgesic action they employed the Martin-Macht method of electrical determination of skin sensibility. They find that such representative analgesics as atophanyl and pyramidon produce uniform bilateral analgesia in normal persons and in those suffering with a considerable variety of nervous diseases. In five patients with extensive thalamic lesions analgesia was found to be produced only upon the side of the body on which the thalamus was normal, skin sensibility being unchanged on the diseased side. On the contrary, morphin produces equal bilateral analgesia in these thalamic cases just as in normal individuals. From these observations the authors conclude that the seat of action of the analgesics such as atophanyl and pyramidon lies in the optic thalamus. Following upon this conclusion it is interesting to note that, through the administration of atophanyl and the discovery of its site action, the authors were able to make a correct diagnosis of a thalamic lesion in a patient otherwise unsuspected.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D., OF PHILADELPHIA.

The Prevention of Tuberculosis in Children.—CASPARIS (*J. Am. Med. Assn.*, 1929, **93**, 1639) advocates tuberculin tests on all school children as a part of a plan for the prevention and control of the disease. In children with positive reactions, the pre-school children of the family should be tested. Investigation into the histories of the adult members of the family should be made and those with suggestive symptoms should be examined carefully in an attempt to find the source of dissemination. This process of finding tuberculosis in all its various stages should be the function of health organizations. The next step would be the distribution of the care of all of these individuals. He feels that success in the prevention of tuberculosis will require the aid of the practising physician who is really the ultimate health officer. Records of the positive tuberculin test, the state of the child's nutrition, including height, weight and age, and of the condition of the tonsils and teeth should be made. This record along with any other available data, such as recommendations for care, should be sent to the family physician. In the same way adults in whom the disease is suspected should be sent to the family physician or if they cannot afford a private physician to some dispensary. The author realizes that the carrying out of such a plan as this would be a tremendous task but he feels that as tuberculosis is a tremendous problem, in spite of the large work it should be attempted and widespread coöperation secured. In order to accomplish this, years of organization may be required. Educational propaganda must be used in schools and in clinics and meetings with physicians and the laity. The tuberculin test is of the greatest importance.

Cereals and Rickets.—Steenbock, Rising, Black and Thomas (*J. Am. Med. Assn.*, 1929, **93**, 1868) made antirachitic active various cereal products such as whole-wheat meal, patent white flour, shredded wheat biscuit, cream of wheat, whole-corn meal, corn flakes, hominy and rolled oats by irradiation with ultraviolet rays. They found that this activity was stable to autoclaving for thirty minutes at 15-pound pressure followed by drying at 60° C. for a few days. Storage for sixteen months at 60° C. or at lower temperature did not cause destruction but after from twenty-three to twenty-eight months there was a decrease in potency. Even untreated cereals kept shorter periods than this became too unpalatable for human use. Household cooking did not have any effect on the antirachitic activity. Vitamin A and the vitamin B complex are labile to ultraviolet radiation but evidence of their destruction in cereals cannot be obtained with such an exposure as is necessary to secure the best antirachitic activation. The commercial irradiation of cereals has been standardized so that the activity induced did not exceed by a multiple of 3 that necessary to form bone of the best ash content. In this way there was prevented any change in palatability, destruction of vitamins and danger of hypervitaminosis. By feeding commercially irradiated rolled oats, rickets was prevented in dogs and rats and no interference in growth of reproduction was shown in the latter over a duration of fifteen months in four generations.

The Early Diagnosis of Appendicitis in Children.—Flusser (*München med. Wchnschr.*, 1929, **76**, 1542) states that in children who are operated on for acute appendicitis it may sometimes be seen that the appendix show the signs not only of an acute appendicitis but also of chronic inflammation and adhesions. Such conditions indicate that the child had suffered previously from appendicitis, but that the condition had not been recognized. In order to detect signs which at the times of the first attack of appendicitis had not been recognized as indications of the disease the author studied the past history of such patients. He found that aversion to eating and loss of appetite were always present. He found as another frequent sign, rectal tenesmus. This was manifested in a desire for defecation but no result following the straining. Vomiting may also be a sign of appendicitis. Limping on the right leg without any evidence of bone or joint disease is suggestive of appendiceal inflammation. The frequent or suppressed urination and the desire to urinate without the passing of urine is almost always a sure sign of appendicitis. One of the difficulties encountered is the difficulty of localizing abdominal pain in children. Abdominal rigidity may not be recognized because of crying. The differential diagnosis is especially difficult in cases of inflammation and other infectious diseases. Umbilical colic often simulates appendicitis.

The Relation Between Colic and Eczema in Early Infancy.—White (*Am. J. Dis. Child.*, 1929, **38**, 935) states that very young infants with true colic or vagogenic gastroenterospasm, in whom eczema develops later are almost three times more numerous than those suffering with either condition alone. Allergic family history is found with about the same frequency in infants with eczema with colic, or with both. The usual sequence is first colic, then diarrhea, followed by vomiting occur-

ring from two to four weeks of age and finally eczema appearing about ten weeks of age. Atropin is effective about three times more frequently in infants with colic alone than in infants with both colic and eczema. In some cases of colic in which atropin produces no improvement, the feeding of thick cereal may be beneficial, but there is no evidence that the feeding of thick cereal predisposes the eczema. Because of hyperacidity that is associated with hypomotility infants with gastroenterospasm seem to tolerate sweet milk better than lactic acid milk. The author believes that exudative diathesis, vagotonia and vagogenic gastroenterospasm with or without eczema are of a common allergic basis.

Interpretation of Roentgenograms of the Chest in Children Based on Observations at Necropsy.—Bigler *Am.* (*J. Dis. Child.*, 1929, **38**, 978) studied the lungs of 171 children coming to necropsy to determine what pathologic changes were present to account for the shadows seen in the roentgenograms of the chest. He feels that it is impossible to formulate any standard for a normal chest for the Roentgen ray standpoint and the interpretation of Roentgen ray pictures should go hand in hand with the history, clinical and physical observations and laboratory data. The hilum shadows and the linear markings are made up for the most part of the blood in the bloodvessels and not of the bronchi. The rounded shadows of even density occurring in the inner third of the lung fields as well as those found along the linear markings are due to bloodvessels running parallel to the actual axilray. Normal lymph glands do not cause shadows. Hypoplastic lymph glands whether caseated or inflammatory, whether in the hilum or intrapulmonary tissue, cannot be recognized as such if they do not contain calcium. They will not cast shadows unless they are large enough to encroach on the pulmonary fields from the mediastinum or from the hilum, or unless they are visible by contrast in the air-filled pulmonary tissue. The size and shape of the shadows at the hilum is influenced not only by active infection but also by the remains of previous infections.

Early Rheumatic Infections of Childhood.—McLean (*Arch. Pediat.*, 1929, **46**, 657) studied 118 patients with early rheumatic infections. Of these 67 were girls and 51 were boys. The largest number of cases was seen between the sixth and seventh years. Histories of repeated attacks of tonsillitis with nasopharyngeal infections were noted in 89 or 75 per cent of the cases. Pains in the legs, joints or stiffness of the limbs was observed in 80 or 60 per cent of the cases. Clinical symptoms or physical signs of a mild chorea were seen in 42 cases of which 27 cases were girls and 15 boys. Soft blowing systolic heart murmurs were heard in 84 or 71 per cent of the cases. Underweight for the height was noted in 103 or 87.3 per cent of the cases whereas underweight for age was noted in 92 or 77.9 per cent of the cases. Of this group of patients 35 developed clinical symptoms and physical signs of rheumatic infection while under observation. The tonsils were considered the foci of infection in 57 cases and 54 or 97.7 per cent of this number had heart murmurs and 7 or 12.2 per cent had evidence of chorea. In 9 children in whom both the tonsils and the teeth were considered the foci of infection, heart murmurs were heard in 6 and there were physical signs and

symptoms of chorea in 6. In 16 cases in which the teeth alone were thought to be the foci of infection there were only 4 patients with heart murmurs, all of whom had had the tonsils removed previously and gave histories of having had repeated attacks of tonsillitis.

Tonsillectomy in Prevention and Treatment of Rheumatism.—FINDLAY, MACFARLANE and STEVENSON (*Arch. Dis. Child.*, London, 1929, **4**, 313) feel that a preliminary tonsillectomy may possibly render and individual susceptible to rheumatic infection but not to chorea. A preliminary tonsillectomy or one performed early during the course of infection may in the case of arthritis render the heart less liable to be attacked but this does not hold true of chorea. As cardiac complications usually develop during the first or second rheumatic attack, the operation, in order to prevent cardiac injury, should be performed prior to a possible second attack. Tonsillectomy in the case of carditis following arthritis seems to have a beneficial effect on the progress of the disease, but this does not hold true in carditis following chorea. The varying behavior in response to tonsillectomy of examples of the rheumatic infection characterized by chorea and by arthritis suggests the possibility of a different strain of the infective organism in these two types of the disease.

DERMATOLOGY AND SYPHILIS

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Previous Treatment of Patients who Have Developed Neurosyphilis.—WEATHERBY (*Am. J. Syph.*, 1929, **13**, 339) takes as his thesis the moot question of influence of specific treatment in syphilis on the incidence of neurosyphilis. His study embraces 280 cases, of which 135 were paresis, 37 were psychoses with cerebral syphilis, 31 tabes dorsalis and 77 cerebrospinal syphilis. Of the paretics, only 16 were definitely known to have had previous treatment and but 2 of these received prompt and adequate arsphenamin therapy. The author concludes that paresis occurs independently of treatment with arsphenamin, and that paresis usually develops in the undiagnosed, the neglected and inadequately treated patients. The author drew no conclusions from his group of psychoses and tabes dorsalis in which there were histories of treatment in 19 per cent and 22.6 per cent. Of the 77 patients with cerebrospinal syphilis, definite knowledge of treatment was recorded in 19 or 25 per cent. The author believes that in this series arsphenamin appeared to predispose to the early onset of cerebrospinal syphilis and points out that neurologic symptoms appeared on an average in less than three years after the primary lesion in the treated cases, while the

symptoms were delayed in the untreated cases to ten years. (The reviewers dissent with the writer on these conclusions and differ with him in his conception of adequate treatment. By generally accepted modern standards, but few, if any, of his patients received adequate early treatment. In the 2 cases cases receiving the maximum number of arsphenamin doses, no note is made of the additional use of mercury or bismuth. The reviewers feel that the maxim "A little treatment may be dangerous" is illustrated and it is rather the lack of *sufficient* arsphenamin rather than the *use* of arsphenamin that constitutes the etiologic factor.)

Retention of Bismuth in the Organism in the Treatment of Syphilis.—LOMHOLT (*Arch. Derm. and Syph.*, 1929, **19**, 891) reviews the literature on the absorption and excretion of bismuth salts by the experimental animal. Intramuscular deposits of bismuth, particularly compounds of low solubility and "oil suspension" are excreted rather slowly by the body. Absorption is determined by two main factors, the chemical formula of the salt and the fineness of the suspended particles in the compounds. Saturation of the tissues with bismuth is of some therapeutic importance, not only because of its effect on the spirochete, but also because of the continuance of this saturation makes it possible to maintain a certain antisyphilitic effect for some time after the cessation of treatment. Most of the reports on direct investigation deal only with storage in the viscera and the quantities are not large although they have the highest concentration of the metal. The occasional investigations on the supporting tissues have revealed rather small concentrations. The total amount of bismuth found in the tissues and organs is but a small fraction of the total quantity injected. Gruhzit, Tendick and Sultzaberger hold a different opinion and believe that for a long period after treatment large quantities are diffused and stored in the tissues. They arrived at this conclusion after determinations on the excretion through urine and feces together with determinations on the excised deposit mass. Later these authors concluded that bismuth is practically fixed in the bone which serves as a storage depot. Lomholt, by a special radiochemical method, using bismuth oxychlorid in both water and oil and working with guinea pigs, determined the amount of bismuth in: (1) The site of injection; (2) the viscera and specimens of the muscular and bone tissue; (3) the rest of the body; (4) the daily excretion of urine and feces. The rate of absorption varied greatly; in 5 cases more than 50 per cent was absorbed after ten days. Small injections seem to be absorbed relatively more quickly than larger ones. The major part of the quantity injected was excreted relatively quickly with the urine and feces. Another large although varying amount remained at the site of injection. Only small quantities were diffused and stored in the tissues making up the "true retention." From seven to ten days later only 4.7 per cent to 13.1 per cent was left. The majority of the retained bismuth was deposited in the abdominal viscera, especially the kidneys, liver and large intestine. The author could not confirm the observation that bone acted as a storage depot. Although weak concentrations, about 1 per cent, were used in this work, and in human therapy concentrations weaker than 5 per cent are not feasible, the author concludes in general that the rate of elimination corresponds well with that of absorption.

GYNECOLOGY AND OBSTETRICS

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Roentgen Therapy of Fibromyomata.—In the course of her twelve years' experience with the Roentgen treatment of uterine fibromyomata HANKS (*Radiology*, 1929, **12**, 403) has found that there are a few questions which are asked so frequently by not only the laity but also by physicians that she answers them categorically. (1) If the tumor is not treated surgically, is there greater danger of cancer? She believes that Roentgen ray is a safeguard against cancer but certainly such women are not more prone to cancer than normal women. (2) Does Roentgen ray therapy injure a woman sexually? She has taken great pains to ascertain the truth on this apparently urgent question. Many of her patients state that since being relieved by Roentgen ray therapy, intercourse has been resumed normally because of absence of pain and the fear of conception. The knowledge that the pelvic organs are intact also helps. It is safe to say therefore, that Roentgen radiation in small doses, not frequently repeated and not continued too long, does not affect sexuality. (3) Will a woman become obese? If the woman is naturally obese, she will probably remain so, and after the menopause she may gain weight, as women did before the Roentgen ray was discovered, but under conservative application of Roentgen radiation she is no worse than she would have been without it. (4) The questions prompted by the perennial fear of burns from the Roentgen ray are many. The fact that she has had no burns nor other accidents in more than twelve years, proves that they can be eliminated.

Roentgen Therapy of Uterine Fibroids.—In presenting his experiences with the Roentgen irradiation of fibroid tumors of the uterus, LINDENBERG (*California and Western Med.*, 1929, **31**, 93) states that the effect of the rays in this condition is due to their effect on the ovaries, namely the production of castration. When considering this type of treatment there are certain contraindications which must be borne in mind. Younger women in whom we wish to preserve ovarian function should not be irradiated. Such patients show better results from myomectomy or hysterectomy. Surgical interference in which the ovaries can be preserved is a lesser insult than a premature menopause with its intense disturbances. Women who wish to have children should also be excluded from radiation therapy. Very nervous women are more benefited by operation with preservation of the ovarian function because in such patients the sudden exclusion of the ovarian hormone often aggravates the unbalanced nervous system. In dealing

with any abdominal tumor difficulties are often encountered in ascertaining the correct diagnosis. There is scarcely a more dangerous agent in the whole field of medical therapy than Roentgen rays if improperly applied. It is very important therefore that the supposed fibroid is not in reality a pregnant uterus, an ovarian tumor or a pyosalpinx. There are also certain types of fibroids which must be excluded. When the tumor is undergoing degeneration it should be removed in order to eliminate the danger of sepsis or peritonitis. In the presence of submucous tumors the bleeding is caused not only by the ovarian influence, but also mechanically by an erosion of the overstretched thin-walled veins in the endometrium. Radiation of such tumors is not only unsuccessful but if the tumor is big and an intensive dose is applied the life of the patient is at times endangered because the irradiation causes an involution of the uterus and an obliteration of the blood supply and possibly a necrosis of the tumor. Large tumors and those causing pressure symptoms should not be irradiated as it will take much too long to obtain the desired effect. Malignant degenerations should usually be excluded from this type of treatment as surgery gives much better results. In brief therefore, those tumors are suitable for Roentgen therapy which are correctly diagnosed uncomplicated fibroids with menorrhagic disturbances. Such tumors are usually of the interstitial variety and will constitute about 25 per cent of all fibroids. As an example of the care which he has exercised in his work it may be stated that he has irradiated 59 patients and refused treatment to 44 in whom he deemed the treatment unsuitable. In 30 per cent of the patients treated the fibroid totally disappeared, in 39 per cent the tumors shrank to less than half their former size and in 11 patients the tumors shrank to about one-third the original size. In about 5 per cent there was no shrinkage of the tumor but amenorrhea was produced with complete relief of symptoms. He believes that if the diagnosis is correct and the cases are properly selected success may be expected in 100 per cent of the cases with no untoward results. In our clinic, where radium is always available, we seldom resort to Roentgen therapy. We believe that the majority of tumors should be treated by surgery, a minority of properly selected cases may be satisfactorily irradiated with radium, while we reserve Roentgen irradiation for those patients who are not fit subjects for surgery on account of constitutional contraindications and whose tumors are too large for radium therapy a diagnostic curettage should precede irradiation by either radium or Roentgen ray.

Vaginal Metastases of Fundal Cancer.—Vaginal metastases which accompany cancer of the uterine fundus have been the object of a study carried on by MEIGS (*New England J. Med.*, 1929, **201**, 155). He found that this condition is not an uncommon lesion since 12 per cent of all cases of fundal adenocarcinoma seen at the Collis P. Huntington Memorial Hospital had such metastasis. Cancer in the vagina should not be regarded as primary there until the uterus has been investigated. These metastases probably take place by way of the lymphatics or possibly by venous channels, while direct implantation is less probable. Hysterectomy is to be preferred when the vaginal metastasis seems treatable and the uterine tumor operable. Radium should be used in the uterine canal and in the metastasis if either the original tumor or the

local metastasis is inoperable or untreatable. Infiltration of the metastasis with gold or glass seeds and a surface application with about 2500 millicurie hours of lead screened radiation is the treatment preferred in dealing with the local vaginal metastasis. In 10 out of 16 cases so treated in this series the growth disappeared while in 6 cases the growth was not favorably influenced. Four proven cases out of 24 who had adenocarcinoma of the fundus with metastatic nodules of carcinoma in the vagina are alive and well nine years, seven years, five years and seven months respectively after treatment. This study indicates the necessity of careful periodic vaginal examination following either hysterectomy or radium treatment of fundal cancer.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Herpes Zoster Ophthalmicus Apparently due to Chronic Frontal Sinusitis.—Herpes zoster ophthalmicus following upon chronic frontal sinusitus appears to be rare. LANDIS (*Penn. Med. J.*, 1929, **32**, 765) reports the case of a man in which the right forehead and region of the right eye was involved. Examination elicited tenderness over the frontal bone and above the internal canthus. The mucous membrane of the nose was greatly congested with enlargements of both middle and inferior turbinates. On the right side there were several polyps and pus was present in the middle nasal passage. The pharynx and tonsils were also congested. The right eyelid was edematous and the conjunctiva very congested. The cornea was not involved. The pupils reacted to light and accommodation, but the left pupil was slightly larger than the right. The retina was normal except for a slight overfilling of the veins. The left eye was normal. A radical operation was done by the Lathrop method, pus evacuated, hyperplastic tissue removed and a drainage tube passed through the nose. The patient improved and the herpetic condition began to dry up on the second day. Two weeks later since pain persisted though the herpetic condition had cleared up the ethmoid cells and the bulla were partially removed together with the anterior tip of the middle turbinate. Some pain and burning still persisted after dismissal; this was probably due to a nerve caught in the scar. It improved under diathermy. Because of the localized nature of the eruption Landis attributed it to peripheral reflex irritation of the supraorbital branch of the superior division of the fifth nerve from chronic frontal sinusitus.

Appearance of Peculiar Petechiæ in the Conjunctiva in Endocarditis Lenta.—Petechiæ with a white center on the conjunctiva have been considered an accidental occurrence in endocarditis lenta. OETTINGER

(*München. med. Wchnschr.*, 1929, **76**, 796), however, investigating them, found that they occurred with extraordinary frequency. They are of varying size, round or spindle-shaped and dark red, more often located on the conjunctiva of the lower then of the upper lid and most frequently on the transitional fold. The white center is really gray-white, is sometimes placed peripherally and sometimes so small as to be visible only with the loupe. Only rarely is it absent. The individual petechia lasts for a few days, gradually paling. For sometimes thereafter a yellowish brown fleck remains. Histologic examination showed that the petechia consisted of hemorrhage with cellular infiltrate (white center). During the past two years in which Oettinger has been looking for these petechiæ they have never been absent from a case (14). They show a periodic appearance and disappearance, not being present at every examination. More often they appear during an exacerbation, but are sometimes found at the beginning of the disease. In 2 cases petechial hemorrhages in the skin and buccal mucosa also appeared shortly before death. In the other 12 cases (6 substantiated at autopsy) the petechial formation was limited to the conjunctiva. Since these hemorrhages often occur in the early stages of the disease and the cutaneous ones do not appear any too frequently and when present usually do not appear until the end stages of the disease, the conjunctival hemorrhages may serve to decide the diagnosis in doubtful cases.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Experimental Herpetic Encephalitis in the Guinea Pig Produced Through the Respiratory Tract.—Having produced herpetic encephalitis experimentally by feeding herpes virus to guinea pigs, McKINLEY (*Proc. Soc. Exper. Biol. and Med.*, 1929, **26**, 699) considered the possibility of infecting guinea pigs by dropping herpetic brain emulsion into the nostrils of these animals. His experiments indicated that, in certain cases, the virus of herpes may reach the brain of guinea pigs following deposition of the virus in their nares. That only a few animals so inoculated became infected is considered by the author to be significant of the fact that even highly virulent strains become attenuated by passage through guinea pigs by the feeding and inhalation methods employed. While practically nothing is known concerning the portal of entry of the true virus of epidemic encephalitis in man, and while there is little evidence to support the view that epidemic encephalitis is caused by the herpes virus, the possibility of infection by such a virus through the respiratory tract may prove to be of importance from the epidemiologic point of view.

Lesions in Nasal Mucous Membranes of Monkeys with Acute Poliomyelitis.—The ease with which monkeys may be infected with poliomyelitis by nasal instillations of virus either with or without preliminary scarifications of the nasal mucosa has been known since the early experiments of Flexner and Lewis. In view of the fact that virus has been demonstrated in the nasal secretions of human "carriers," STEWART and RHOADS (*Proc. Soc. Exper. Biol. and Med.*, 1929, **26**, 664) examined histologically the nasal mucosæ of monkeys dying of acute poliomyelitis to ascertain if any demonstrable changes were evident. No lesions suggestive of any specific character were seen in the deeper structures of the nose. However, in 17 of the 31 monkeys with experimental poliomyelitis, interesting lesions, consisting of isolated necroses of the epithelial cells of the respiratory (nasal) mucosa were encountered; along with an acidophilic degeneration of the nuclear chromatin, leading to an appearance strongly suggesting inclusion bodies—the nature of which is uncertain. The authors are of the opinion that further study is required to determine whether these intranuclear acidophilic bodies are inclusions in a specific sense.

Further Consideration of Transmissibility of Human Upper Respiratory Infections (Common Cold) to the Ape.—SHIBLEY, MILLS and DOCHEZ (*Proc. Soc. Exp. Biol. and Med.*, 1929, **27**, 59) some time ago reported upon the suitability of the anthropoid ape as an experimental animal for study of the common cold, because of the fact that the upper respiratory flora of these animals resembles closely that of humans, and these animals are very susceptible to colds when exposed to human beings suffering from such infections. They showed that nasal washings obtained from humans suffering with typical colds produced the same symptoms in the apes when injected intranasally. They now discuss the importance of control experiments which would not be adequate unless they were carried out in a period of the year when ordinary colds were at a minimum, because of the possibility during the months in which colds are present of using filtered nasal washings from individuals apparently well, but who might be carriers of the active agent. These control experiments consisted of a repetition of the transmission experiments of the previous winter, using nasal washings in healthy individuals who had had no colds for at least three months and who were not exposed to colds during that time. Control experiments gave absolutely negative results and were seen to prove definitely that the earlier transmission experiments were definitely positive, indicating that the type of upper respiratory infection under consideration is caused by filtrable virus.

Studies in Asthma. IV. The Nose and Throat in Asthma.—With the idea of finding the part played by focal infections and other disturbances of the nose, throat and teeth in asthma of all kinds, RACKEMANN and TOBEY (*Arch. Otolaryngol.*, 1929, **9**, 612) reviewed the data of 1074 asthmatics—28 per cent of whom had had operations on the nose and throat without regard to the cause of asthma as found. A true focus of infection in the nose, throat and teeth was encountered in 44 per cent of all cases, while vasomotor rhinitis occurred in 14 per cent. As one would expect, there were more patients with an infective focus in the *intrinsic*

than in the *extrinsic* group. It was learned that the presence of these foci have little relation to the outcome of the asthma. After outlining the treatment of these various foci, the authors observed that the gross results of this treatment were disappointing, as shown by the comparison of patients with foci in each group on whom operations were and were not performed, and by analysis of the different lesions treated; and that local treatment of the nose, throat and teeth apparently had afforded permanent relief from asthma in 5 per cent of cases. The absence of demonstrable infection in the contents of "infected" sinuses in two instances suggested that local lesions of the nose and throat may develop from the same fundamental cause as the asthma itself and be part of the pathologic process of the disease.

The Pathogenesis of Cholesteatoma.—Suppurations of the middle ear are the commonest conditions encountered by the otologist; and the most important of these are the chronic types associated with the formation of cholesteatoma. It is recognized that cholesteatoma begins as an epidermization of the lining of the cavity of the middle ear and may take place by one of several different methods. As a rule the epidermization occurs following the destruction of the normal middle-ear mucosa and tympanic membrane, seen so frequently after an acute exanthematous otitis media or a chronic process such as tuberculosis of the middle ear. In either event it has been accepted generally that a relatively long period elapses between the initial suppuration and the formation of cholesteatoma. In reporting the clinical and microscopical findings of a case of fulminating scarlet fever, with spontaneous rupture of the tympanic membrane on the sixth day and death from septicemia a week later, POLVOGT (*Arch. Otolaryngol.*, 1929, **9**, 597) found a distinct ingrowth of squamous epithelium from the external auditory canal with a beginning cholesteatoma of the tympanic cavity. He states that this is the earliest known formation of this growth (seven days after a spontaneous marginal perforation from an acute necrotic scarlatinal otitis). In the light of these pathologic findings, the author emphasizes the advisability of performing a radical operation in both the acute and chronic (usually tuberculous) forms showing cholesteatomous formation.

Agranulocytic Angina. A Report of Three Cases with Necropsies.—In 1922, Schultz described a series of cases of gangrenous stomatitis associated with a marked leukopenia affecting chiefly the granular leukocytes. Since then many similar instances have appeared in the literature of this country and abroad, so that in 1928, Hueper was able to collect about 125 recorded cases. While agranulocytic angina is the term most commonly applied to this condition, some prefer the name *agranulocytosis*, and Hueper referred to it as *agranulocytosis* (*Schultz*). In presenting the clinical and necropsical data of 3 cases (in one of which the authors were not entirely convinced of its agranulocytic anginal character), THOMAS and SERVICE (*Clifton Springs Med. Bull.*, 1929, **15**, 219) were able to confirm many of the outstanding features of the disease, namely, the gangrenous stomatitis, the grave leukopenia (often as low as 1000 and sometimes nearer 100 white cells per c.mm.), the paucity or absence of granular leukocytes, the diminution of polymorphonuclear leukocytes in the exudate in the bronchopneumonia,

and the total absence of cells of the myelocyte series in the bone marrow. The onset of agranulocytosis is usually sudden, being ushered in by sore throat and fever. The course of the malady is rapidly progressive, the patients becoming extremely ill and septic. Coma ensues early and death often takes place in five to ten days. Many different types of microörganisms have been isolated, but no one organism, or group of organisms, have been found to be constantly present. It is inferred from these facts that the breaking down of the bodily resistance, due in part to the loss of polymorphonuclear leukocytes, permits bacteria to invade the tissues. In other words, the specific cause of agranulocytic angina is unknown at the present time.

RADIOLOGY

UNDER THE CHARGE OF

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Intrapelvic Protrusion of the Acetabulum.—Eight cases of inward protrusion of the acetabulum are reviewed by Doub (*Radiology*, 1929, **12**, 369). The condition is rare, though first described more than a hundred years ago. Its cause has not been ascertained, and several factors are probably concerned. Osteoarthritis is a common accompaniment, and this may be a late stage of some general disease in early life causing softening of the bones with the resultant deformity. Clinical findings refer mostly to pain and restriction of normal motion of the hip. The Roentgen picture discloses a deepening of the acetabulum with thinning of the mesial and inferior wall and bulging of the acetabulum into the pelvis. The head of the femur is therefore more deeply buried, and the greater trochanter is somewhat higher and closer to the acetabulum.

A Roentgenologic Consideration of Duodenitis.—In 1921, Judd directed attention to duodenitis, a diffuse inflammation of the duodenum, with or without actual ulceration. His observations have been confirmed from the histopathologic standpoint by MacCarty, Konjetzny and Wellbrock. Kirklin (*Radiology*, 1929, **12**, 377) reviews the findings in 45 cases observed recently at the Mayo Clinic. This series indicates that duodenitis is characterized roentgenologically by marked irritability of the bulb, which tends to empty itself quickly but not completely. It is best recognized during the period of emptying; the bulb does not empty in a normal even manner, but a spastic, grossly-deformed, skeleton-like cap is seen, although it may appear normal

during the filling phase and while full. The deformity differs from that of typical ulcer in that its borders are less sharply defined, no marginal or central niche can be seen, and there is no gastric retention. Its positive distinction from frank ulcer is not yet feasible, and it might be confounded with reflex spasm of the bulb, but it seems to warrant further study.

Endothelial Myeloma.—Nine cases of endothelial myeloma are reviewed by KIRKLIN and WEBER (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 355). The oldest patient was twenty-nine, the youngest patient two and a half years; the average being eleven years. All the patients except one were males, and they were mostly of asthenic build. Bones involved were: the femur in 4 cases, fibula in 2, tibia in 1, humerus in 1 and scapula in 1. In the long bones the disease seemed to prefer the upper portion of the shaft. Roentgenologically it is characterized early by a translucent area, corresponding to the tumor, in the medulla; the tumor enlarges, expands and destroys the cortex and invades the soft tissues. A striking feature in the cases here reported was a fine-meshed gauze-like shadow in the invaded soft tissues, due apparently to an effort at periosteal repair. Osteomyelitis and osteosarcoma may enter into the differential diagnosis.

Early Diagnosis of Perforated Peptic Ulcer.—A case of perforated ulcer near the pylorus is reported by GEIER (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 465) in which free intraperitoneal air was demonstrated with the Roentgen ray within ten minutes after the perforation occurred. The air was visible as a rarefied space between the dome of the liver and the under surface of the diaphragm, also between the diaphragm and the abdominal viscera on the left side. In every case of perforation of the stomach or duodenum free gas and fluid are present in the peritoneal cavity. Search for this evidence with the Roentgen ray should not require more than five minutes, since the patient can be placed before the roentgenoscope while still on the hospital carriage, and no special preparation or contrast meal is necessary.

Indications for Radiation Therapy in Benign Uterine Hemorrhage.—The prime indication for radiation therapy in benign diseases of the uterus according to SCHMITZ (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 327) is hemorrhage, but this is subject to qualifications. Infections, displacements, traumas, and accidents of pregnancy call for either medical or surgical treatment. The necessity of a correct diagnosis before treatment is begun is emphasized, and in all doubtful cases immediate diagnostic curettage or excision of suspected areas of tissue for microscopic examination is imperative to rule out malignancy. No treatment is required in myomas not causing symptoms. Radium treatment is indicated in myomas causing hemorrhage: (*a*) if they are free from complicating infection, especially adnexitis; (*b*) if they are not associated with complicating pelvic diseases requiring surgery, such as ovarian tumors; (*c*) if they are not larger than a four-month pregnancy; (*d*) if they are not degenerating; (*e*) if they are not growing rapidly; (*f*) if they are located intramurally; (*g*) if they are not complicated with a severe anemia out of proportion to the symptoms and

clinical findings; (*h*) if they are not causing pressure symptoms; (*i*) if they occur in patients thirty-six years of age or older; (*j*) if they do not occur in persons with personal or familial neurotic tendencies; (*k*) if there is no doubt about the diagnosis. Less than 11 per cent of the cases of myomata in Schmitz's series were treated by irradiation, and the treatment of choice is surgery. The predominant method of treatment in hypermenorrhea due to atonicity and hypoplasia of the uterus was medical. The medical treatment consisted in the use of ergot, hydrastis, pituitary extract from the anterior lobe, adrenalin, regulation of food and exercise. If medical treatment failed then dilatation and curettage were employed, and if the latter failed irradiation was used. Contraindications to irradiation, however, are: (1) coexisting infections such as adnexitis and pelvic peritonitis; (2) patients under thirty-six years of age; (3) neuropathic tendencies.

Use and Abuse of Physical Therapy in Chronic Arthritis.—In the opinion of STONER and BROOKHART (*Arch. Phys. Ther., X-ray, Radium*, 1929, **10**, 149) physical therapy should be used only as an adjunct and not independent of accepted general measures of treatment in the management of the chronic arthritic. This implies an accurate diagnosis and a rational classification of the various clinical manifestations of the disease. The authors admit that in a series of 140 cases of chronic arthritis, baths, massage, ultraviolet ray and diathermy were used with considerable disappointment in certain cases. In the whole group of chronic diseases, perhaps none are more difficult to treat than chronic arthritis; any or all forms of treatment yield unsatisfactory results at times. Diathermy, which occasionally seems to have value, more often is disappointing, and in the more acute cases seems to be contraindicated. In the treatment of this group of 140 cases, effort was made to improve the general health. A relatively low-carbohydrate was advised in most cases, and a low-caloric intake in the obese. Rest, avoidance of exercise and encouragement of elimination was the routine in all cases. Drug therapy comprised the salicylates, cinchophen, iodides, amido-oxylbenzoate, and in the obese with a low-metabolic rate thyroid extract was judiciously administered. Colonic irrigations were used as a routine. Marked improvement followed in 14 per cent, definite improvement in 61 per cent, no improvement in 8 per cent, and 10 per cent were questionable.

Physical Measures in the Treatment of Pain.—When the local production of pain is the result of a toxin carried to the part, there are two plans of treatment, according to BEHAN (*Arch. Phys. Therap., X-ray, Rad.*, 1929, **10**, 390); one is to deaden receptivity of the nerve itself and the other is to remove the toxin. In the first method ice may be applied, in the second method heat. Throbbing pain in all inflammations, whether septic or otherwise, can be very definitely relieved by a Bier hyperemia bandage applied above the inflamed area. Pain produced by movement, as in joints, is relieved by immobilizing with splints. Painful scars can frequently, by the use of the Roentgen ray, be softened and then permanently eradicated by the use of the ultraviolet light and diathermy. The galvanic current is useful in cases of painful sphincter contraction, especially in cases of anal fissure. Overdilatation of the

anal sphincter, the vesical sphincter, or the os uteri, with or without anesthesia, is often of value in relieving painful conditions. Joint distention is a common cause of pain in certain varieties of arthritis; compression over the joint with a large dry bath sponge held in place by a bandage is often effective; the sponge may also be moistened with a saturated solution of magnesium sulphate. Hyperextension of the thigh sometimes relieves sciatica, and diathermy is beneficial. The Roentgen ray can be employed in many cases of terminal nerve pain due to toxemia, in reflex pain and in neuritis. The ether spray is useful in many cases of referred pain, especially pain associated with the cranial nerves.

Surgical Procedures in Carcinoma of the Rectum.—RANKIN (*Radiology*, 1929, **13**, 207) notes that at the Mayo Clinic the cases of carcinoma of the rectum are arbitrarily divided into two distinct groups, the operable and the inoperable, the former being recommended for surgery, the latter for palliative operation, radium and Roentgen ray, or irradiation alone. The presence of absence of metastasis and the degree of malignancy as graded after Broders' method, affect the result from either procedure. In a large series of cases, when metastasis was present operation yielded good results in approximately 20 per cent only; when it was absent operation was effective in more than 57 per cent. The results obtained in cases in which malignancy was graded 1, with metastasis, were almost as good as in cases in which malignancy was graded 3 and 4, without metastasis. The average duration of life after operation decreased as the grade of malignancy increased. Grading of malignancy aids in the selection of cases for treatment by operation or radium or both. Malignant growths of grade 3 or 4 are more radiosensitive than those graded 1 and 2.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Congenital Auditory Imperception (Congenital Word Deafness): With Report of a Case.—WORSTER-DROUGHT and ALLEN (*J. Neurol. and Psychopath.*, 1929, **9**, 193) present a case in which a boy, aged twelve years, was unable to understand speech by auditory perception but who showed no evidence of deafness and was able to carry out commands by lip reading. The case was complicated to some extent by a certain degree of word blindness as well. There was no defect of

hearing and the muscles of articulation were intact. The peripheral organs of sight were also normal. The patient would often repeat words as he heard them and repeat them many times with no obvious appreciation of their meaning. It was also noticeable that he did not recognize mistakes in music that were very gross and was not disturbed by discords. He could not repeat correctly a number of musical notes sung in his hearing. On the evidence presented they conclude that there is a complete absence of memory for words and musical tones. The patient was unable to use words spontaneously until he had acquired the art of lip reading. The authors then branch into a discussion of "centers" for word memory and conclude, because of the development by the patient of a language of his own, that while the auditory and visual centers for words were not normally developed, and while the center for the memory of words from lip reading was just developing, it would be inevitable that he would develop idioglossia. The idioglossia in this case represents an extreme form of mispronounced and ill-expressed conventional language. They conclude that the case illustrates the interdependence of each and every elementary part of speech mechanism and especially the dependence of normal speech development upon the appreciation of variations in sounds. They believe that the speech mechanism cannot be divided into clearly defined "centers" but must be regarded as a physiologic mechanism which functions as a complete whole. As to the cause of this disorder they consider the balance of evidence to be in favor of a biological variation or of a local aplasia but state that birth injury cannot be definitely excluded.

The Relation of the Spirocheta Pallida to the Pathological Changes of Dementia Paralytica.—SMYTH (*J. Ment. Sci.*, 1928, **74**, 687) attempts to correlate all the clinical and pathologic factors of dementia paralytica. Fifty-two cases of general paralysis, a few cases showing syphilitic changes in the cerebral arteries and two apparently normal brains for control purposes were examined. The patients had all been followed clinically. Spirochetes were found in 38 cases (72 per cent) of general paralysis by use of Jahnel's stain. They were not found in any of the other cases. They were found in the gyrus rectus in 32 cases; prefrontal, 34; psychomotor, 27; temporal, 26; visual, 5. Of the cases in which spirochetes were found in the visual region 2 were of the juvenile type. They were found most readily in fairly rapid subacute cases and in the childish, emotional, euphoric types and cases of the melancholia type. In very acute cases with mental confusion and rapid exhaustion and in the slow, dull, confused type with progressive dementia the spirochetes were absent or occurred in scanty numbers. Chronic cases showed a similar variation, those of the grandiose or emotional type showing spirochetes in large numbers, those of the confused, demented variety having few or none. He finds that convulsive and paralytic attacks have no relation to the number of spirochetes present. He discusses at length the lymph circulation in its relation to path of infection and believes that the subacute cases are lymphogenous in origin while the more acute cases are probably hematogenous. He believes that because of the toxicity of the cerebrospinal fluid, nervous tissue is not likely to be a favorable medium for the growth of spirochetes and he would

account for the alterations in the period of incubation of the organism in nervous tissue on this basis. The vascular changes in general paralysis, he finds to be not dependent on the local presence of the spirochete but to be part of a general pathologic change. The same contention he holds for cerebral wasting which he believes takes place in the cerebrum in reverse order to that of the evolution of its parts. He finds a distinct correlation between the presence of spider cells and neuroglia fibers in the deeper cortical layers and the presence of spirochetes. Cellular infiltration of the cortex with neuroglial cells, plasma cells and lymphocytes is also associated with the number of spirochetes present. In view of the clinicopathologic relationships advanced here he finds an interesting association with the fact that the best results of therapy by malaria inoculation and tryparsamid have been obtained in grandiose cases and in those with agitated melancholia, while in the confused and demented types little or no improvement has followed. He believes that infection of the central nervous system takes place early in the course of syphilis and advises routine examination of the cerebrospinal fluid in early cases. "A well known pathologist has recently made the surprising statement that lumbar puncture is not justifiable in cases of early syphilis since only 2 per cent show any change in the cerebrospinal fluid, yet it is a significant fact that only 2 per cent of all cases of syphilis develop general paralysis, thus it is not unlikely that cases of early syphilis which show changes in the cerebrospinal fluid are potential paretics, and it is to such cases that our present therapeutic methods might, with advantage, be applied."

Dystonies.—AUSTREGESILO and MARQUES (*Revue Neurologique*, 1928, **2**, 562) present a discussion of the intermittent spasmodic dystonies. They consider that these cases represent a variety of conditions which can be divided primarily into pure dystonies and dystonic states. In the latter the symptoms of dystony are mixed with signs of other lesions of the central nervous system such as Wilson's disease, pseudosclerosis, double athetosis, and various encephalopathies of children. From a review of the literature and their own pathologic studies they conclude that in general the lesions are in the region of the striate body. They present 5 cases in some detail. They feel that the dystony may appear slowly and progressively at puberty with a progressive degeneration resembling Wilson's disease or perhaps may occur as the result of infectious illness often after epidemic encephalitis in which case one can usually demonstrate other concomitant syndromes. A study of the clinical and pathologic findings in these conditions has been greatly furthered by the occurrence of epidemics of encephalitis which have greatly increased the numbers of cases to be observed. Contrary to former opinions that the dystonies were encountered only in Russian or Polish Jews they have collected a number of cases in a great variety of races and their own cases occurred in both native and Spanish Brazilians.

An Apparatus for the Induction of Muscular Relaxation and Sleep.—ROSETT (*Arch. Neurol. and Psychiat.*, 1929, **22**, 737) describes an apparatus, the action of which is to produce a wave of encircling pressure applied to the periphery of the body and limbs in the direction of the

venous flow. By using this apparatus he obtained muscular relaxation and, in most persons, sleep which he ascribes to a physiologic state of nerve inhibition. He finds that patients subjected to the action of the apparatus a number of times appear to contract a habit of relaxation in that they rest better at night and go about their business and pleasure in a more deliberate and systematic manner and show a general improvement in nutrition. During the action of the apparatus the blood pressure, both systolic and diastolic, is reduced in certain cases, especially in those with high blood pressure, but remains unaltered in others and in some cases shows a reduction at certain times and not at others.

PATHOLOGY AND BACTERIOLOGY

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Prenatal Volvulus of Small and Large Intestine Caused by a Mesenteric Cyst.—Owing to the various types of structure which may appear as cysts between the layers of the mesentery of the small intestine confusion has arisen in efforts to classify them. SALA and NACHAMIE (*Arch. Path.*, 1929, **8**, 180) suggest the classification of purely enterogenous cysts, which they believe originate in a process of sequestration during embryonic life, into: (1) Cysts in the wall of the intestine; (2) cysts extending into the mesentery; (3) cysts extending into the lumen of the intestine. They report a case of enterogenous cyst which arose before the descent of the cecum and produced a prenatal volvulus of the small and large intestine in a full-term, female, colored child. The cyst, oval in shape, measuring 8 cm. in its longest diameter, and included between the leaves of the mesentery, was contiguous along the line of attachment of the mesentery with a loop of small intestine which was stretched and flattened over it. There was an obstruction of the jejunum above the tumor. The cyst wall was formed by mucosa, inner circular and outer longitudinal muscle layers and serous coat. The inner circular muscle layer of the cyst split to encircle the adjoining intestine at the junction of cyst and bowel and the outer longitudinal layer was common to both. In view of these histologic observations they suggest that such a cyst should be treated by resection of the involved loop of bowel.

Leukocyte Content of Regional Lymphatics in Inflammation.—MENKIN and FREUND (*Arch. Path.*, 1929, **8**, 263) were able to collect and study the lymph, draining an area of inflammation produced in the foreleg of the rabbit by the injection of sterile irritants. While it was demonstrated that the cellular content of a comparable normal lymph-

atic vessel in the rabbit consisted almost entirely of lymphocytes, polymorphonuclear leukocytes always appeared in the efferent lymphatic vessels of the regional lymph node of the inflamed area. Monocytes and clasmatocytes were also frequently observed in the lymphatics draining the area, but their presence was less constant than that of the polymorphonuclears. The inflammatory reaction studied by microscopic sections, was observed to have involved the regional lymph node as well as the site of injection. It is pointed out that in inflammation the lymph circulation offers a path of return of some of the migrated leukocytes to the blood stream.

Undulant Fever in the United States.—There has appeared in the last few years a very extensive literature on undulant fever, indicating a greatly increased incidence, and although it is possible, it cannot be positively asserted that this is due to its recognition and separation from formerly obscure fevers. BLUMER (*Ann. Int. Med.*, 1929, **3**, 122) has pointed out that the increase has not occurred among persons connected with the goat industry, and only a few infections have been related to porcine or human contact. The vast majority of cases, however, have occurred in people not in contact with goats or hogs but rather with cow's milk. Nevertheless, the evidence suggests that it is of porcine rather than of bovine origin. This means that a great deal more must be known of the epidemiology of this disease before, as the author emphasizes, any laws or regulations for its control are put into effect.

Changes in the Intestinal Flora After Partial Gastrectomy.—Many untoward effects in the general physiology of the digestion have been explained as the result of interference with the gastric secretions particularly in various grades toward achlorhydria. PORTIS (*Surg., Gynec. and Obst.*, 1929, **48**, 470) finds that subtotal gastrectomy results in a change in the upper intestinal flora of dogs so that it comes to assume the fecal character of the lower intestine. These changes did not follow gastroenterostomy and as the other technical procedures were the same the negative results are useful controls to indicate the dominance of the altered gastric secretions so that there is a loss of bactericidal activity, a more rapid emptying time of the stomach and an alkaline medium in the jejunum.

HYGIENE AND PUBLIC HEALTH

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Undulant Fever.—HARDY (*J. Am. Med. Assn.*, 1929, **93**, 891) presents some of the salient points in the knowledge of undulant fever.

He states that the characteristics of Brucella melitensis have only recently been fully described. A classification of strains isolated from human beings cannot now be regarded as a reliable index of the importance of the different varieties as a cause of human disease. A special effort should be made to obtain a detailed postmortem study in all fatal cases of undulant fever. The pathologic lesions and clinical signs of Brucella melitensis infections in animals show a definite correlation. The epidemiologic data, based on the reports of more than a thousand recent cases of undulant fever in the United States, indicate that cattle and hogs with contagious abortion are the source of these infections. Macroscopic agglutination tests on patients with febrile illnesses of undetermined etiology should be made more frequently. Additional study is essential in order to determine effective and applicable methods of control. KING (*New England J. Med.*, 1929, **201**, 918), who has made a study of Brucella abortus infection of milk, states that contagious abortion is widely prevalent in cattle throughout the United States, and that approximately 20 per cent of raw market milk is infected with Brucella abortus. Both bovine and porcine strains are pathogenic for man. It is impossible to specify any given serum agglutinin titer as diagnostic of undulant fever. Ingestion of infected milk and direct contact with infected animals are the chief causes of undulant fever. Either universal pasteurization of milk or a new code of certification of milk is essential in the control of undulant fever. That undulant fever is a public health problem is indicated by the increasing number of cases being reported.

Cancer Studies in Massachusetts. III. Cancer Mortality in Nativity Groups.—LOMBARD and DOERING (*J. Prev. Med.*, 1929, **3**, 343) state that a sufficiently close correlation exists between the social classes in England and the nativity groups in Massachusetts in respect to the cancer death rate to warrant the opinion that economic social conditions are a factor in the causation of cancer. The foreign born have much higher rates than the native born of native parents in cancers of the buccal cavity and the stomach. Cancer of the stomach is abnormally high among both males and females for all foreign-born groups, and cancer of the buccal cavity among the Irish, English and Teutons. Cancer of the lower intestinal tract in females is high among the Irish and English, while it is low among the Italians. The Canadians have a high rate for cancer of the uterus, and the Russians a low rate. Both the Italians and the Russians have low rates for cancer of the breast. The Irish and the Italians show higher rates in Boston than in their native countries. The sex ratio (females per male) is much higher for the native born of native parents than for any of the foreign nativity groups which have been studied in Boston and Europe. The Irish have slightly poorer diagnostic facilities than the other foreign groups, but the foreign born taken as a whole have sufficiently good diagnosis to eliminate the factor of diagnosis in discussing the high cancer death rate of the foreign born.

Leprosy in the United States.—A statistical study of 700 cases in the National Leprosarium: Hopkins and Denney (*United States Pub. Health Rep.*, 1929, **44**, 695) summarize their study as follows: A statistical study of 718 lepers hospitalized over a period of 34 years in the Louisiana Leper Home, later the National Leprosarium, was made. Two hundred and fifteen were foreign born, and 503 were natives of the United States. The present population of the hospital is 287. Mexico, China, Italy, Greece, and the Philippine Islands have furnished one-half of the total foreign born. Most of the lepers came from Louisiana, California, New York, Texas and Florida; 418 came from Louisiana. The incidence of leprosy among the white population of Louisiana is computed to be twice that in the negro. Of the total cases, 11 per cent were of the nerve type, 39.1 per cent of the skin type, and 49.9 per cent of the mixed type. Of the total cases, 72.3 per cent were in males and 27.7 per cent were in females. The social status of the patients represents a cross section of the normal populace. The average age at onset of the disease is computed as 30.2 years; the average age on admission to the hospital was thirty-six years, with an average period of six years prior to admission, during which time each patient may have been a menace to public health. In a group of 100 Louisiana lepers, hospitalized more than fifteen years ago, it has been disclosed from subsequent records that in 64 instances only one leper in the family developed the disease, while in the 36 other instances leprosy occurred in 83 additional relatives. In some families the disease has invaded certain branches to the point of extermination. Instances of familial transmission have also been noted in cases from other States than Louisiana. It has not invariably happened that the parent became infected before child; indeed, the reverse frequently occurred. Intimate contact over a period of time extending into years has been concurrent in most instances of familial transmission; in many cases multiple contacts also existed. In 5 cases the incubation period is calculated as not less than six years. The first manifestation of leprosy was recalled by most patients as one or more spots appearing on the face; in no instance were conditions described that might be identified as prodromal symptoms or as the initial lesion of leprosy. Aside from the increased number of cases developing in males at about twenty-one and in females at about nineteen years, and the counterbalancing rarity of leprosy before the age of nine years, the disease appears to manifest itself at all ages about equally. The duration of leprosy is computed as approximately fourteen years. It appears that leprosy greatly shortens the life expectancy of the young, but has less effect on the life expectancy of the aged. The mortality rate has gradually decreased in the hospital since its organization. Leprosy *per se* has been the cause of death in less than 20 per cent of the lepers; respiratory, renal, and cardiac disorders indirectly dependent on leprosy have caused more than one-half the deaths. Before rigid rules for paroles were promulgated, relapses of discharged cases were not uncommon; but in the last seven and a half years 28 lepers have been paroled and only 1 has relapsed and been readmitted.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 16, 1929.

Energy Expended in Maintaining a Muscular Contraction.—D. W. BRONK (Eldridge R. Johnson Foundation, University of Pennsylvania). The recent work of ADRIAN and BRONK (*J. Physiol.*, 1928, **66**, 81; 1929, **67**, 119) has shown that the grading of a reflex or voluntary muscular contraction depends largely on a change in frequency of the motor nerve impulses. This frequency was found to vary from as low as 5 or 10 to 100 a second, which would indicate that a weak contraction is maintained by asynchronous series of twitches in the several muscle fiber groups, while a strong response is produced by a fused tetanus of the active fibers. In order, therefore, to determine the economy of energy expenditure in maintaining contractions of varying strengths the heat production and tension time have been measured at various frequencies of stimulation. As the rate of stimulation is increased, the economy or amount of tension-time maintained per unit of energy expended increases. This is primarily due to a greater degree of fusion of the separate muscle twitches, there being no increase in economy with frequencies of a value higher than that needed to produce complete tetanus. It may be concluded, therefore, that tension is maintained with a smaller expenditure of energy in a strong contraction than in a weak one.

It is a well-known fact that a stimulation frequency not quite sufficient to give partial summation of the successive twitches will, if continued, produce a fused tetanus. This altered character of the response is due to progressive fatigue. In order, therefore, to determine the economy of maintaining tension throughout the development of fatigue, a muscle has been stimulated in nitrogen at a frequency of about five a second for a period of three minutes and the rate of heat production and tension time developed has been measured. The results of these experiments show that a unit of tension is maintained with a lower expenditure of energy as the muscle fatigues. This fact is of probable importance in connection with long-sustained contractions.

The Influence of Electrolytes on Certain Types of Hemolysis.—M. H. JACOBS (Department of Physiology, University of Pennsylvania.) Although the mammalian erythrocyte is structurally a very simple type of cell whose properties might be expected to remain fairly constant under a variety of external conditions, it is, in reality, extremely sensitive to slight changes in its environment. Certain striking effects of low concentrations of salts upon hemolytic processes are here reported.

In the case of simple osmotic hemolysis where the entrance of water into the erythrocyte is the factor chiefly involved, low concentrations on nonelectrolytes of the order of 0.01 or 0.02 M have a barely detectable effect. Hemolysis in such solutions is almost as rapid as in distilled water. To double the time required to reach a certain degree of hemolysis in solutions of nonelectrolytes concentrations of the order of magnitude of 0.10 M are necessary. In the case of electrolytes, on the other

hand, a noticeable retarding effect was found with the following concentrations: NaCl, 0.001 M; $CaCl_2$, 0.0001 M; Al_2Cl_6, 0.00004 M, while the time for hemolysis was doubled in 0.005 M, 0.0012 M and 0.0002 M solutions, respectively.

The effect of salts on the rate of osmotic hemolysis involving the penetration of a dissolved substance as well as water may sometimes be of a different nature. Thus, the time required for human erythrocytes to reach 75 per cent hemolysis in 1 M glycerol was in a typical experiment diminished by 0.01 M NaCl from 245 to 110 seconds and that for ox erythrocytes to reach 83 per cent hemolysis in 0.125 M glycerol was similarly diminished by 0.0025 M NaCl from 332 to 11 seconds. In experiments of this type involving hypotonic solutions an apparent retarding effect on the penetration of water and an apparent accelerating one on the penetration of glycerol may coëxist and give to the entire process a considerable complexity. The accelerating effect of salts on hemolysis by penetrating substances seems to be limited to compounds like glycerol which penetrate with difficulty.

Neutral salts also have a very pronounced accelerating effect on hemolysis by certain concentrations of acids. The time of penetration of 0.012 N HCl from isotonic nonelectrolyte solutions into erythrocytes, as judged by the color change produced by the formation of acid hematin within the cells, is considerably accelerated by small amounts of NaCl and $CaCl_2$. The effect of Na_2So_4 on penetration is similar to that of NaCl and $CaCl_2$ but certain concentrations of this salt greatly retard hemolysis or prevent it altogether.

The Contractility of the Gall Bladder.—I. S. RAVDIN, (Department of Research Surgery, University of Pennsylvania). Several methods have been used in order to determine whether or not the gall bladder is capable of emptying its contents through the cystic duct. If the bile which once enters the cystic duct does not leave the gall bladder by the same route, bile pigment should be present either in the cystic lymph vessels or an increase in bile pigment should be obtained in the cystic vein blood. The cystic lymph fluid of the dog or cat does not contain bile pigment nor does the cystic vein blood contain a larger amount of this than is present in the peripheral venous circulation. That the gall bladder can empty materials (carbon particles or dyes) through the cystic duct can be demonstrated by placing these materials in the gall bladder after ligating all ducts, other than the cystic duct, which enter the common duct and then stimulating gall bladder contraction either by a fat meal or by drugs. The substances can then be found in the duodenum. The isolated gall bladder of the dog, guinea pig, and rhesus monkey have been studied in a constant temperature bath (38.5° C.). They all show rhythmic contraction and respond to certain drugs as one would expect. Histamin, pilocarpin, physostigmin and barium chlorid cause an increase in tonus while adrenalin and atropin cause a relaxation of the muscular activity.

Intraperitoneal and Intrapleural Pressure Relationships.—RICHARD H. OVERHOLT (Department of Research Surgery, University of Pennsylvania). A method was devised for the insertion of a cannula through the anterior abdominal wall into an intraperitoneal space and through the chest wall into the intrapleural cleft so that the variations in intra-

pleural pressure coincident with abdominal manipulations could be studied. Anesthetized and unanesthetized dogs were used. A water manometer and a membrane manometer which was later calibrated were used to register pressures. It is impossible to register the true intraperitoneal pressure by the method used, but the method served as a basis of comparison with similar types of procedures which have been carried out by other investigators. On introducing the cannula into the abdomen, the pressure at the point of measurement was always found to be subatmospheric. With the dog in the head-up position, the subatmospheric pressure increased with the cannula in the epigastrium. In the head-down position and the cannula in the same position, the subatmospheric pressure approached atmospheric pressure or became slightly positive. By the method used it was impossible to record marked variations in intraperitoneal pressure after manipulation of the abdominal wall or distention of the stomach or colon unless pneumoperitoneum was present. However, abdominal manipulations with or without the presence of pneumoperitoneum affected the intrapleural pressure. After pneumoperitoneum, the intraperitoneal pressure was increased greatly by the application of an abdominal binder, inflation of the stomach, or a shift in position. The presence of small amounts of air in the peritoneal cavity had little or no effect on respiratory movements or on the intrapleural pressure. If 50 cc. or more air per kilogram were injected intraperitoneally, the amplitude of the intrapleural tracing was increased and the intrapleural pressure at the end of expiration approached atmospheric pressure. The rate of respiration was increased. Incision of the abdominal wall caused a decrease in rate and an irregularity of the excursions. The intrapleural pressure at the end of the expiratory phase approached atmospheric pressure or became slightly positive. The application of pressure or a binder to the abdomen affected the intrapleural pressure to a greater extent when air was present within the peritoneal cavity. The same holds true for the effect of inflation of an intragastric balloon. Phrenic nerve stimulation increased the subatmospheric pressure in the pleural space on the same side. Vagal stimulation stopped respiration with equal pressures in the two pleural cavities.

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